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HEREDO-RETINOPATHIA CONGENITALIS

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A Genetical-Statistical Study by

CARL HENRY ALSTRÖM

In Clinical Collaboration with

OLOF OLSON

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HEREDITAS

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Monohybrida Recessiva Autosomalis

A Genetical-Statistical Study

by

CARL HENRY ALSTRÖM

Laboratory no. 2 for Human Genetics,
the Psychiatric Clinic of the Caroline Institute,
Stockholm

In Clinical Collaboration

with

OLOF OLSON

The State Institute for the Blind,
Tomteboda, Stockholm

LUND 1957

Translated by

Erica Odelberg

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TO

TORSTEN SJÖGREN

in Honour

of his 60th Birthday

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PREFACE

This investigation could not have been carried out without the financial support given by »Statens medicinska forskningsråd» and »Stiftelsen Therese and Johan Anderssons minne».

My sincere thanks are due to the Vicars of the various parishes, who have given me invaluable help. I wish in particular to express my appreciation to the Rev. NILS JOËLSON for his great interest, and for his comprehensive and inestimable assistance in the genealogical investigations.

I owe a great debt of gratitude to my friend and former assistant at the Laboratory, the late Dr. NILS LINDGREN. His unselfish, skilful work and unfailing interest during many years' cooperation have been of the utmost value, especially in carrying out the extensive genealogical studies.

I should also like to express my appreciation to many competent assistants at the Laboratory, in particular to Mr. RALPH MARTENS, Mr. OLOV STOCKMAN, Miss TANJA KARLQUIST and Med. stud. TORGNY ALSTRÖM.

My gratitude is also due to Mrs ERICA ODELBERG, who has spared no pains over the translation into English.

It is a pleasure to acknowledge my great indebtedness to my coworker in the clinical part of the work, Dr. OLOF OLSON, Ophthalmologist to Tomteboda Institute, for his excellent cooperation over many years, which has been the very basis of the investigation. Together we offer our warm thanks to Professor GÖSTA KARPE, Head of the Eye Clinic, Karolinska Sjukhuset, for valuable discussions, for his great consideration with respect to the electroretinographic examinations and for cataract operations on two patients carried out in his clinic. We are also indebted to his assistants at the electroretinographic laboratory, Miss ANN-MARI EKANDER and Mrs INGER KÖNIG, for their skilful help.

Our profound thanks to Professor TORSTEN SJÖGREN for his unceasing encouragement and support throughout the course of this somewhat arduous investigation are expressed on a preceding page of this monograph.

Stockholm, 1956. *Carl Henry Alström*

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INTRODUCTION

In 1945, ALSTRÖM's attention was drawn by TORSTEN SJÖGREN to the occurrence at Tomteboda Institute for the Blind of cases with the diagnosis of congenital retinochoroiditis, which seemed to show a familial incidence and a high frequency of first-cousin marriages in the parents. Such cases had been noticed by SJÖGREN more than 25 years earlier, in the course of his now classical work on juvenile amaurotic idiocy.

In order to obtain an idea of the frequency of these cases, ALSTRÖM made, in this year, a first study of the registers and case records at Tomteboda Institute, and a preliminary registration of the probands and their families. The results indicated that strong reasons existed for investigating whether this might be a genetically uniform disease group, which did not seem hitherto to have been described in the literature.

In the spring of 1946, ALSTRÖM contacted Dr. OLOF OLSON, the ophthalmologist at Tomteboda Institute, and enlisted his cooperation in the clinical-ophthalmologic part of the investigation. A comprehensive inventory was made of all the patients admitted to the Institute, particularly after 1897, it being in this year that education of blind children who had reached school age was made compulsory in Sweden. Since 1946 we have been engaged, at Laboratory 2 for Human Genetics at the Psychiatric Clinic, Karolinska Sjukhuset, in tracing the proband and secondary families thus registered, and in making a thorough genealogic investigation of them.

Our criteria in selecting the probands were the following:

1. The diagnosis retinochoroiditis, not due to any known cause, made by the ophthalmologist in attendance at the Institute. In addition, cases with the diagnosis amaurosis or amblyopia congenita, also without known cause, and in which no objective ophthalmologic changes could be observed, despite the highly defective vision. The reasons for thus enlarging the original proband definition emerged at an early stage of the investigation. Firstly, persons with this diagnosis were found as secondary cases in the proband families. Moreover, a large number of

these patients later exhibited so-called retinochoroidal changes and were then given the first-mentioned diagnosis.

2. Congenital blindness or defective sight, or such observed during the first year of life.

3. Apart from the impairment of sight, absence of neuro-psychiatric and general physical disease.

In 1946—48 ALSTRÖM and OLSON made a thorough neuro-psychiatric and ophthalmologic examination of all the pupils then attending Tomteboda Institute (both its primary and elementary school) with blindness observed during the first year of life, irrespective of the diagnosis and cause. During these years, ALSTRÖM also started to make field investigations over the whole country, in order to investigate the proband families traced: parents, sibs and children. In two of these investigations in southern and central Sweden, ALSTRÖM was accompanied by Dr. NILS LINDGREN, assistant at Laboratory 2 for Human Genetics. Two field investigations were subsequently made in central and southern Sweden by Dr. OLSON. Affected persons encountered during the field investigations were later summoned to Stockholm for further ophthalmologic examination by him.

In 1949—50, the work at Laboratory 2 for Human Genetics was dominated by essentially other tasks; this also applied to the greater part of 1946—48. It was not until 1951 that full attention could once more be devoted to the present investigation, which was completed in 1956.

The electroretinographic examinations were made at the ERG laboratory of the Eye Clinic, Karolinska Sjukhuset, where two of the patients also underwent operation for removal of complicating cataract. Electroencephalography was performed at the EEG laboratories of the Psychiatric and Paediatric Clinics of Karolinska Sjukhuset. A large number of data regarding examination of the patients at other hospitals and institutions were also collected, as well as results of examination by other physicians.

The final clinical and statistical analysis of the group of patients investigated — comprising about 10 per cent of all the pupils admitted to Tomteboda Institute — showed the following features to be common to them, their affected sibs and other secondary cases:

(a) Probably congenital defect of sight.

(b) At an early age, as a rule scanty fundus changes or none at all, despite highly defective vision.

(c) Existing fundus changes of a relatively uncharacteristic appearance.

(d) As a rule, absence of any neuro-psychiatric or endocrinologic complications. In the few cases in which they were present, they were evidently a chance finding.

The final genetic-statistical analysis of the group of patients assembled on this clinical basis showed chiefly the following:

1. A familial incidence of this rare phenomenon in sibs.
2. A high frequency of consanguineous marriages in the parents.
3. Distribution over the whole country, but some tendency to accumulation in certain regions, with about one-fourth of the total 105 families investigated belonging to a few large family complexes.

These facts, taken together with certain population statistical calculations, make it highly probable that a presumably uniform, genetically determined disease with a low frequency in the population has been detected.

A study of modern textbooks, *e. g.* that of DUKE-ELDER, and of recent genetic-ophthalmologic literature, has failed to disclose any description entirely compatible with the disease or disease group in question. FRANCHISCHETTI, SORSBY and WARDENBURG are among the most distinguished of modern writers on ophthalmology from the genetic viewpoint, and have done pioneer work in this field. Both SORSBY's »Classification of the Unassociated Dystrophies of the Fundus» and his »Genetics in Ophthalmology» give an instructive survey of present-day conditions, with a register of existing dominant, recessive and sex-linked dystrophies (*cf.* SORSBY, 1948, p. 111). The condition in question here is not specifically listed among them.

In a study of the older literature, it was found that LEBER, in 1869 and 1871, described a disease which he denoted as »Congenital Amblyopie» or »Amblyopie in Folge von Ret. pigmentosa». Judging by his account, at any rate some of his cases seem to have been identical with the disease group studied in the present investigation. However, 4 out of his 14 patients also had impaired hearing, a feature that was not present in our cases.

The present investigation was, in its entirety, organized at, and directed from, Laboratory 2 for Human Genetics, at the Psychiatric Clinic, Karolinska Sjukhuset. The statistical analyses of both the genetic and the clinical data were performed there by ALSTRÖM.

I

Material

TO facilitate understanding of the present material and of the problems of its representativeness, it is desirable to have some knowledge of the organization for the education and care of the blind in Sweden. A detailed account of this already has been given by SJÖGREN and LARSSON (1949) in »Microphthalmos and Anophthalmos with or without Coincident Oligophrenia». Here, only certain aspects will be touched on.

In 1897, an Act was passed enforcing the central registration of blind children, and their compulsory education. Those with no complicating handicap are assigned to Tomteboda Institute for the Blind in Stockholm. This comprises both a primary school, covering the first four years' schooling, and the Institute itself, corresponding to the four-year elementary school education. This may be followed by further vocational training at the Institute. Until 1935, there was also a primary school in Växjö, from which the children were sent to complete their education at Tomteboda Institute. For admission to either of the primary schools and to the Institute, a medical certificate testifying to good mental and physical health, in addition to impairment of sight, was required. Since 1935, the only primary school is that at Tomteboda.

Admission can also be gained to the Institute, without passing through the primary school, by pupils who have attended an ordinary primary school in their home district, but have subsequently been referred to education for the blind. It was apparent from SJÖGREN and LARSSON's investigation that registration of blind children was formerly not complete at the age of compulsory schooling (7 years), but only two years or so after this age.

The intellectual requirements for being able to benefit from education at the Institute have been fairly high. Children who have not fulfilled these requirements have been sent for further education, of a special-class nature, to the Asylum in Lund. This institution has also provided

for the care of blind persons with a severe complicating disability (mental disease or severe oligophrenia), *e. g.* cases of juvenile amaurotic idiocy. Thus, cases with a complicating disability have not, other than exceptionally, passed through Tomteboda Institute, but have been admitted direct to the Asylum in Lund.

In addition to the educational organizations for the blind outlined in the above, there is a vocational training school for blind men in Kristinehamn and for blind women in Växjö. Until 1935, a similar school for women existed in Uppsala.

On the basis of the registers, admission certificates, case records and ophthalmologic case records for each case, a central register was set up at Laboratory 2 for Human Genetics at Karolinska Institute for all pupils admitted to Tomteboda Institute (*i. e.*, its elementary school) from its opening in 1873 up to and including 1954. A central card index was made for the years 1897 to 1948 inclusive. This comprised 1,132 pupils, 656 males and 476 females. Of these 1,132 pupils, 624 (55 per cent) were totally or partially blind from birth or observed during the first year of life. The distribution of these cases by year of admission to the elementary school of the Institute is shown in Table 1. The follow-

TABLE 1. *Pupils admitted during 1897—1948 to the Secondary School at Tomteboda Institute for the Blind.*

Ap=amblyopia et amaurosis congenita, A=atrophia n. opt., R=retino-choroiditis, Ap_p (8) and R_p (10) indicate probands or propositi, A_s (9) indicates secondary cases belonging to the A group (5).

(1) Year of admission	(2) Total	(3) Congenital impairment of sight	(4) Ap	(5) A	(6) R	(7) Σ	(8) Ap_p	(9) A_s	(10) R_p	(11) Σ
1897—1898	36	22	—	—	—	—	—	—	—	—
1899—1903	120	67	—	13	7	20	—	5	5	10
1904—1908	90	44	2	4	5	11	1	2	5	8
1909—1913	130	67	6	2	9	17	4	—	7	11
1914—1918	118	62	1	3	12	16	—	1	11	12
1919—1923	108	60[1]	—	—	14	14	—	—	12	13[1]
1924—1928	125	68	4	1	13	18	4	—	12	16
1929—1933	120[2]	68	4	1	14	19	4	—	12	17[2]
1934—1938	111	55	3	3	8	14	3	—	7	10
1939—1943	93[3]	56	7	—	7	14	7	—	7	15[3]
1944—1948	81	55	7	4	8	19	7	1[4]	7	15[4]
	1132	624	34	31	97	162	30	9	85	127

[1–3] Secondary cases F63b, F73b, F76b. [4] F91a.

ing larger diagnostic groups may be distinguished, included in column (3). a) Malformations, albinism, microphthalmos, etc. b) Opacities of the media, errors of refraction, cataract, ectopia lentis, keratomalacia, aphakia, etc. c) Inflammatory lesions of known cause, syphilitic and non-syphilitic. d) Hydrophthalmos, buphthalmos, corneal staphyloma, etc. — Of these only one case (cataract F 76 b) is included in the present investigation, and as a secondary case.

The following cases included in column (3) are also recorded separately. Cases with the diagnosis of amblyopia or amaurosis congenita without demonstrable fundus or other changes are recorded in column (4). Cases with the diagnosis of optic nerve atrophy are listed in column (5) and those with lesions of the retina and/or choroid in column (6), in both groups without stated cause. In some cases the statement »on a hereditary basis» had been added, quite unsystematically, to the diagnosis. A notation of this kind in the records from the Institute has not been allowed to influence the subsequent classification or selection of the cases. — The groups listed in columns (4) to (6) are denoted as Ap, A and R, respectively.

It is from these three groups that the Institute cases included in the present study are derived. Their number is recorded in columns (8), (9) and (10). In column (11) is the sum of these three groups. These figures include two secondary cases with the diagnosis of retinochoroiditis, in which the impairment of sight was stated to have been observed at two and three years of age, respectively (see further p. 42), and one case of congenital blindness but with bilateral cataract which prevented inspection of the fundi. It was not possible to obtain definite information as to whether the cataract was congenital or had not developed until later.

Altogether 127 cases are included in the investigation, *i. e.* about 11 per cent of the pupils admitted to the Institute between 1897 and 1948 inclusively.

At the beginning of the investigation, the proband criteria covered only cases of congenital blindness, or blindness observed during the first year of life, with »retinochoroiditis». It was soon found that the proband families also included cases with the diagnosis of amblyopia or amaurosis congenita without demonstrable fundus changes, at any rate initially. Consequently, as stated in the Introduction, these diagnosis were also included in the proband definition.

Of the 34 pupils admitted to the Institute during 1897 to 1948 registered as cases of amblyopia or amaurosis congenita without known

cause and without demonstrable fundus changes, 30 are included in the investigation as primary probands. They are recorded in column (8) with the denotation Ap_p, and in Table 3 under their Family number as well.

The following four cases of congenital amblyopia were not included. In TI 486, there were reasons to ascribe blindness to a birth injury, and in TI 566 to meningitis. TI 589 passed through the Institute in error, on the way to an institution for cases of severe oligophrenia. She belonged to a sibship with three cases of infantile amaurotic idiocy of atypical development. In TI 769, extensive parenchymatous keratitis was also present which did not, however, entirely explain the severe impairment of vision.

Of the 97 cases in group R, 85 consist of cases with the diagnosis of congenital retinochoroiditis without known cause, and are included in the material as primary probands. They are recorded according to their year of admission in column (10) with the designation R_p, and in Table 3 (p. 26) under their Family number.

The remaining 12 cases, not included in the final material, but appearing in column (6), and belonging to group R, are as follows. TI cgh, with the diagnosis of retinochoroiditis; investigation showed that the disease could probably be ascribed to congenital syphilis. TI 400 and 1129 were typical cases of disseminated choroiditis. TI 788 had cataract of the left eye and a large atrophic focus in the choroid of the right eye. TI 1240 was a case of retinitis punctata albescens. TI 1345 had the diagnosis of central retinochoroiditis and severe myopia. TI 908, 1034 and 1095 were cases of retinitis pigmentosa, the first two examples of the recessive, the last of the dominant form.

There can be little doubt that it was correct to omit these cases. Whether the following three cases should not have been included in the material investigated is less certain. TI 623, admitted to Tomteboda Institute in 1912, had cataract of the right eye and the diagnosis retinochoroiditis in the left. The investigation was, however, complicated by the fact that post-traumatic detachment of the retina was present in the latter eye. His parents were first-cousins. His monozygotic twin brother had also been blind from birth, but he had died at an early age and had not been medically examined. Owing to the uncertainty of the data, this family was not included in the material. — TI 646 had the diagnosis of bilateral retinochoroiditis and was admitted to Tomteboda Institute in 1913. In contrast to the other cases included in the investigation, in which the tension of the eyeballs was normal according to the examin-

ation on admission, he had soft, atrophic eyeballs. — TI 723 was admitted to Tomteboda Institute in 1916, with the diagnosis retinochoroiditis. At the time when the probands were assembled, this patient's case record had been mislaid. It was not found until much later, after the central card index had been set up, and for this reason the patient in question was not included in the material, although he probably belonged to it.

The primary probands thus registered, 30 Ap cases in column (8) and 85 R cases in column (10), altogether 115 probands, represent 90 proband families with an additional 34 secondary cases. Of these, the following were registered at Tomteboda Institute between 1897 and 1948 under the diagnosis of optic nerve atrophy: F. 31 a, F. 43 a, F. 48 a, F. 94 c and F. 85 a (with operated cataract as well). The 34 secondary cases also include the two cases of retinochoroiditis, F 63 b and F. 73 b, in which visual impairment was stated to have been observed at two and three years of age, respectively (see further p. 42), and F. 76 b with cataract, mentioned earlier. Also counted among the 34 secondary cases are three registered only at the primary school at Tomteboda during the stated period, *i. e.*, F. 9 a, F. 47 a and F. 76 c.

A survey of the 90 proband families according to the stated criteria, registered at Tomteboda Institute during the 1897 to 1948 period, is given in Table 2 (p. 17), in which the families are listed from north to south according to their geographic occurrence. In the table the following 15 families are also listed.

In addition to these 90 proband families thus registered, a further 15 families included in the total material are recorded in the survey (Table 2). As actual secondary families to the 90 proband families, the following nine were traced by means of the genealogical studies and field investigations: F. 5, 15, 20, 22, 32, 41, 54, 64 and 70. Of these families, five were registered at Tomteboda Institute, with pupils admitted either before 1897 (F. 20, 41 and 64, the second of which is also represented by one pupil after 1897), or after 1897 (F. 5 and 70). The records for these early cases were scantily worded; all had the diagnosis bilateral optic nerve atrophy. In one early secondary case, TI 63 belonging to F. 64, both an ophthalmologic case record and a diagnosis were lacking. The patient was born in 1867 and was stated, both in the documents relating to admission and by the sibs traced, to have been blind from birth.

Of these nine secondary families in the strict sense, F. 15, 22, 32 and 54 were not registered at Tomteboda Institute. The affected children

TABLE 2. *Survey of the sibships of the affected individuals by county of origin from north to south.*

Column (1): number of family and individual. Column (2): sex. Column (3): P=proband, *i. e.*, admitted to Tomteboda Elementary School between 1897 and 1948, those admitted in 1947—1948 belonging to its Primary School in 1946. S_1=secondary case, pupil at Tomteboda Institute, its Primary School or Elementary School. S_2=secondary case, pupil at another school or institution for the blind. S_3=secondary case, not a pupil at any school or institution for the blind. U=unaffected. Column (4): age at end of 1946. Column (5): d=dead, a=alive.

The bracketed letters between columns (1) and (2) denote that the relevant family belongs to the family complexes R, S, D, A (D and A related to each other), De or Su, respectively. A bracketed figure in the corresponding place denotes relationship with the family having this number. The following families are related by pair: 50—85, 52—101, 54—55, 64—65, 69—70, 80—81; no relationship demonstrated but originating from the same parish: 59—60.

The affected members of each family are listed first in the columns. Their position in the birth series is given in brackets between columns (2) and (3). The unaffected members are then listed according to their position in the birth series of the sibship.

An italicized family number denotes that the parents are first cousins.

(1)		(2)		(3)	(4)	(5)	(1)		(2)		(3)	(4)	(5)
1 a	(R)	m	(3)	P	46	a	j		m		U	40	a
b		m	(6)	S_2	41	a	k		m		U	36	a
c		f	(8)	S_3	37	a	4 a	(R)	f	(1)	P	13	a
d		f		U	51	a	5 a	(R)	f	(1)	S_1	16	d
e		m		U	43	d	b		m		U	52	a
f		m		U	45	a	c		m		U	50	a
g		f		U	43	a	d		m		U	48	a
h		m		U	39	a	e		f		U	47	a
i		m		U	35	a	f		f		U	45	a
j		f		U	33	a	g		m		U	43	a
2 a	(R)	f	(2)	S_2	56	a	h		f		U	38	a
b		m	(4)	P	51	a	i		m		U	35	a
c		f		U	60	a	j		f		U	34	a
d		m		U	54	a	6 a	(R)	f	(1)	P	36	a
e		f		U	49	a	7 a		m	(1)	P	47	a
f		m		U	46	a	b		f	(2)	P	45	a
g		m		U	46	a	c		f	(6)	S_3	3	d
3 a	(R)	m	(1)	P	57	a	d		m	(8)	P	34	a
b		m	(2)	S_3	4	d	e		m		U	44	a
c		m	(3)	S_3	4	d	f		m		U	42	a
d		m	(4)	S_2	6	d	g		f		U	39	a
e		m	(10)	S_4	3	d	h		m		U	35	a
f		m		U	29	d	i		f		U	31	a
g		m		U	4	d	j		f		U	28	a
h		m		U	25	d	8 a	(S)	f	(1)	P	14	d
i		m		U	42	a	b		m	(2)	P	25	a

(1)		(2)		(3)	(4)	(5)
c		m	(9)	P	12	a
d		f		U	24	a
e		m		U	22	a
f		m		U	20	a
g		m		U	19	a
h		m		U	17	a
i		f		U	16	a
j		f		U	11	a
k		m		U	9	a
9 a	(S)	f	(1)	S_2	33	d
b		f	(7)	P	17	a
c		m		U	34	a
d		f		U	30	a
e		m		U	28	a
f		f		U	23	a
g		m		U	20	a
10 a	(S)	f	(9)	P	7	a
b		f		U	29	a
c		f		U	26	a
d		f		U	24	a
e		m		U	23	a
f		m		U	21	a
g		m		U	19	a
h		m		U	16	a
i		f		U	12	a
11 a	(S)	m	(1)	P	39	a
b		m	(3)	P	36	a
c		m		U	38	a
d		f		U	32	a
e		f		U	28	a
12 a	(S)	f	(1)	P	33	a
b		m	(2)	S_2	32	a
c		m		U	29	a
13 a		m	(4)	P	43	a
b		m		U	48	a
c		m		U	6	d
d		f		U	44	a
e		m		U	38	a
f		m		U	37	a
g		m		U	36	a
h		f		U	35	a
i		m		U	33	a
j		m		U	32	a
14 a	(D)	f	(1)	P	20	a
15 a	(D)	m	(3)	S_3	66	a
b		m	(4)	S_3	64	a
c		m		U	71	a
d		m		U	68	a
e		f		U	61	a
f		m		U	58	a
16 a	(D)	m	(1)	P	50	a
17 a	(D)	f	(1)	P	40	a
b		f		U	37	a
c		m		U	2	d
18 a	(A)	f	(1)	P	24	a
19 a	(A)	m	(1)	P	18	d
b		m		U	56	a
c		f		U	20	d
20 a	(A)	f	(3)	S_1	21	d
b		m	(4)	S_1	24	d
c		m		U	5	d
d		m		U	41	d
e		m		U	64	a
21 a	(A)	f	(2)	P	17	d
b		m		U	57	a
c		f		U	53	a
d		m		U	50	a
e		m		U	48	a
f		f		U	44	a
22 a	(A)	m	(1)	S_2	17	d
b		m	(3)	S_2	29	a
c		m	(5)	S_2	25	a
d		f		U	31	a
e		f		U	26	a
23 a	(A)	f	(3)	P	54	a
b		f		U	54	d
c		f		U	67	a
d		m		U	53	a
e		f		U	51	a
f		m		U	18	d
g		f		U	22	d
24 a		m	(1)	P	16	a
b		m		U	14	a
25 a		m	(1)	P	18	a
b		f	(2)	P	16	a
26 a		m	(2)	P	23	a
b		f	(3)	P	21	a
c		f		U	28	a
27 a		m	(1)	P	27	a
b		m		U	18	a
28 a		f	(3)	S_1	8	a
(b		m	(7)	S_3	born in 1949	)
c		m		U	11	a

	(1)		(2)		(3)	(4)	(5)
d		f		U	9	a
e		m		U	7	a
f		m		U	5	a
g		m		U	3	a
29 a		f	(1)	P	35	a
b		f		U	33	a
c		f		U	29	a
d		f		U	27	a
e		f		U	25	a
30 a		f	(4)	P	51	a
b		f		U	70	a
c		m		U	67	a
d		f		U	63	a
e		f		U	42	d
31 a	(Su)	m	(1)	S_1	55	a
b		f	(5)	P	10	d
c		m		U	53	a
d		m		U	39	a
e		f		U	43	a
32 a	(De)	m	(2)	S_3	35	a
b		f	(3)	S_3	31	a
c		f		U	37	a
33 a	(De)	f	(1)	S_2	53	a
b		m	(3)	S_3	48	a
c		f	(6)	S_3	30	d
d		f	(8)	P	33	d
e		m		U	50	a
f		m		U	46	a
g		m		U	2	d
h		m		U	23	d
34 a	(De)	m	(1)	P	15	a
b		m		U	11	a
35 a		f	(1)	S_1	9	a
36 a		m	(2)	P	20	a
b		m	(4)	P	12	a
c		f		U	23	a
d		m		U	15	a
e		m		U	10	a
37 a		m	(1)	S_1	9	a
b		m		U	7	a
38 a	(Su)	m	(6)	P	22	a
b		m		U	33	a
c		m		U	30	a
d		m		U	29	a
e		m		U	2	d
f		m		U	25	a
g		m		U	21	a

	(1)		(2)		(3)	(4)	(5)
h		m		U	15	a
i		f		U	10	a
39 a	(Su)	m	(2)	P	9	a
b		m		U	11	a
40 a	(Su)	m	(2)	P	30	a
b		f		U	32	a
41 a	(Su)	m	(3)	S_1	49	d
b		m	(9)	S_1	54	a
c		f		U	74	d
d		m		U	74	a
e		f		U	51	d
f		f		U	67	a
g		m		U	65	a
h		f		U	63	a
i		f		U	59	a
42 a		m	(1)	P	24	a
b		f	(3)	P	14	a
c		m		U	22	a
43 a		f	(1)	S_1	50	a
b		f	(4)	P	44	a
c		f		U	49	a
d		m		U	47	a
e		m		U	42	a
44 a		f	(1)	P	29	a
b		f	(2)	P	24	a
45 a		f	(6)	P	47	a
b		m		U	59	a
c		f		U	57	a
d		f		U	55	a
e		f		U	53	a
f		m		U	51	a
g		m		U	46	a
h		m		U	43	a
46 a		f	(2)	P	52	a
b		m	(3)	P	51	a
c		f		U	54	a
d		m		U	44	a
47 a		f	(2)	S_1	8	d
b		m	(3)	S_2	2	d
c		m	(5)	P	24	a
d		f		U	35	d
e		m		U	26	a
f		m		U	20	a
48 a		m	(6)	S_1	43	d
b		f	(8)	P	13	d
c		f	(10)	P	49	a
d		f		U	44	d

(1)	(2)	(3)	(4)	(5)
e	m	U	69	a
f	f	U	9	d
g	m	U	65	a
h	f	U	4	d
i	f	U	56	a
j	f	U	51	a
49 a	m (1)	P	25	a
50 a (85)	m (1)	P	25	a
b	m	U	23	a
51 a	f (2)	P	29	a
b	f	U	32	a
52 a (101)	m (3)	P	14	a
b	m	U	24	a
c	f	U	19	a
53 a	f	P	27	a
b	m	U	37	a
c	f	U	14	d
54 a (55)	m (2)	S_3	23	a
b	f (3)	S_3	18	a
c	f (6)	S_3	3	a
d	m	U	12	d
e	f	U	15	a
f	m	U	10	a
55 a (54)	m (2)	P	13	a
b	m	U	16	a
56 a	f (3)	P	42	a
b	f	U	3	d
c	f	U	47	a
d	f	U	41	a
e	m	U	37	a
57 a	f (4)	P	34	a
b	f	U	39	a
c	m	U	37	a
d	m	U	36	a
e	f	U	31	a
f	m	U	22	d
g	m	U	20	a
58 a	f	P	30	d
59 a (60?)	f (1)	P	9	a
b	f	U	7	a
c	f	U	1	a
60 a (59?)	m (1)	P	30	a
b	f (2)	P	29	a
c	m	U	4	d
d	m	U	24	a
e	m	U	22	a
f	f	U	19	a

(1)	(2)	(3)	(4)	(5)
61 a	f (1)	P	26	d
b	f (3)	P	35	a
c	m	U	37	a
62 a	m (1)	S_3	3	d
b	f (2)	P	40	a
63 a	f (5)	P	30	a
b	f (6)	S_1	28	a
c	m (7)	P	26	a
d	f	U	39	a
e	f	U	37	a
f	f	U	35	a
g	m	U	2	d
64 a (65)	m (1)	S_1	27	d
b	m	U	74	a
c	m	U	72	a
d	m	U	68	a
65 a (64)	m (2)	S_2	24	d
b	f (5)	P	29	a
c	m	U	37	a
d	f	U	34	a
e	m	U	32	a
66 a	f (6)	S_1	38	d
b	m	U	26	d
c	m	U	48	a
d	m	U	46	a
e	m	U	44	a
f	m	U	42	a
g	f	U	36	a
h	f	U	34	a
67 a	f (1)	P	18	a
b	f	U	1	a
68 a	m (1)	S_2	19	d
b	f (3)	P	37	a
c	f	U	47	a
69 a (70)	f (2)	P	19	a
b	m (4)	P	14	a
c	m	U	21	a
d	m	U	17	a
70 a (69)	m (4)	S_1	29	d
b	m (6)	S_3	8	d
c	f	U	7	d
d	m	U	61	d
e	m	U	60	d
f	m	U	28	d
71 a	m (2)	P	54	a
b	f	U	36	d
72 a	m (1)	P	32	a

	(1)		(2)		(3)	(4)	(5)
b		m		U	27	a
73 a		f	(4)	P	19	a
b		f	(5)	S_1	17	a
c		f		U	23	a
d		m		U	22	a
e		m		U	21	a
74 a		f	(2)	P	19	a
b		f		U	23	a
75 a		m	(1)	P	34	a
b		f		U	28	a
c		f		U	25	a
76 a		m	(4)	P	40	a
b		m	(5)	S_1	38	a
c		f	(7)	S_1	36	a
d		m		U	1	d
e		f		U	32	d
f		m		U	26	d
g		m		U	38	a
h		f		U	36	a
77 a		m	(1)	P	22	a
b		m		U	19	a
78 a		f	(1)	P	49	d
79 a		m	(1)	P	43	a
b		f	(5)	P	33	a
c		m		U	32	d
d		f		U	39	a
e		f		U	38	a
f		f		U	27	a
g		f		U	26	a
80 a	(81)	m	(2)	P	10	a
b		m		U	3	d
c		m		U	9	a
d		m		U	3	a
81 a	(80)	m	(4)	P	48	a
b		m	(6)	P	45	a
c		f	(8)	P	20	d
d		f		U	54	a
e		f		U	52	a
f		f		U	50	a
g		m		U	47	a
h		f		U	43	a
82 a		f		P	9	a
83 a		f	(1)	P	28	a
b		f		U	26	a
c		f		U	22	a
d		m		U	15	a
84 a		m	(1)	P	36	a

	(1)		(2)		(3)	(4)	(5)
b		f		U	42	a
85 a	(50)	m	(1)	S_1	46	a
b		m	(4)	P	38	a
c		m		U	10	d
d		m		U	41	a
86 a		m	(2)	P	11	a
b		m	(3)	S_2	7	a
c		m		U	1	a
87 a		f	(1)	P	33	a
b		m	(3)	P	29	a
c		f	(4)	P	26	a
d		m		U	30	a
88 a		f	(2)	P	9	a
b		f		U	10	a
c		m		U	6	a
d		m		U	4	a
e		m		U	2	a
89 a		f	(8)	P	13	a
b		f		U	32	a
c		m		U	31	a
d		f		U	28	a
e		m		U	26	a
f		f		U	23	a
g		m		U	21	a
h		f		U	19	a
90 a		f	(3)	S_3	4	d
b		m	(5)	P	29	a
c		f		U	35	a
d		f		U	33	a
e		m		U	31	a
f		f		U	27	a
g		m		U	25	a
h		f		U	24	a
i		m		U	21	a
91 a		f	(1)	S_1	5	a
b		m	(2)	S_3	9	a
92 a		f	(1)	P	12	a
b		f	(2)	P	10	a
c		m		U	7	a
93 a		f	(1)	S_2	9	d
b		m	(2)	P	24	a
c		m		U	22	a
d		f		U	19	a
94 a		m	(2)	S_2	62	a
b		f	(3)	S_3	59	a
c		f	(6)	S_1	31	d
d		m	(8)	P	46	a

(1)	(2)	(3)	(4)	(5)	(1)	(2)	(3)	(4)	(5)
e	m	U	64	a	b	m	U	15	a
f	m	U	56	a	c	f	U	14	a
g	m	U	54	a	d	m	U	11	a
h	m	U	36	d	100 a	f (2)	P	34	a
i	m	U	46	a	b	m (4)	P	29	a
j	f	U	45	a	c	f	U	36	a
95 a	f (1)	S_2	26	a	d	m	U	32	a
b	m (3)	P	11	a	e	m	U	27	a
c	f	U	25	a	101 a (52)	m (1)	P	16	a
d	m	U	7	a	b	m	U	7	a
96 a	f (3)	P	14	a	c	m	U	3	a
b	m	U	28	a	102 a	f (3)	P	37	a
c	m	U	24	a	b	f (5)	P	34	a
97 a	f (7)	P	25	d	c	f (6)	S_2	31	a
b	m	U	37	d	d	m	U	40	a
c	f	U	58	a	e	m	U	39	a
d	f	U	57	a	f	f	U	36	a
e	f	U	55	a	g	m	U	29	a
f	m	U	50	d	*103* a	f (1)	P	42	a
g	m	U	8	d	104 a	f (3)	S_1	8	a
98 a	f (1)	P	42	d	b	f	U	14	a
b	f	U	51	a	c	m	U	12	a
c	m	U	43	a	105 a	m (3)	P	40	a
99 a	f (1)	P	16	a	b	f (5)	P	35	a

were, for various reasons, deprived of the compulsory education to which they were entitled on account of their highly defective vision (see Table 3). This was brought about by a combination of the parents' opposition and laxity on the part of the relevant local authorities. F. 15 belonged to the registration period before 1897. The secondary cases in F. 22 and 32 were born during the 1911—1920 period. Those in F. 54 were born in 1925, 1928 and 1943, respectively. They, as well as the cases just mentioned, were listed in the local parish registers, but had nevertheless succeeded in evading the now very strict supervision by the organization for the blind.

An additional six families registered at Tomteboda Institute for the Blind — the remainder of the aforementioned 15 families — are included in the investigated material, but are not denoted as proband families, on the following grounds. The selection of patients from the stated 1897—1948 period was, in fact, based on admission to the actual Institute (elementary school). In the course of 1946 to 1948, however, *all* pupils attending the Institute were investigated; thus, even those attending the *primary school.* Those who, during the stated period, had

reached the Institute (elementary school) were denoted as primary probands. Of these, F. 28 a, F. 35 a, F. 37 a and F. 104 a, all with the diagnosis congenital amblyopia, had not got as far as the Institute by the end of 1948. Objections can scarcely be raised to the inclusion of these cases, but rather to their exclusion. Nor can any objection be raised to the inclusion of an early primary school case, TFs 154 in F. 66, who was withdrawn from further instruction just before starting at the Institute. The diagnosis was bilateral retinochoroiditis of the relevant type. — F. 91 a was admitted to the Institute in 1948, suffering from optic nerve atrophy of the secondary type and is listed in column (9) of Table 1 (p. 13). The initial inclusion of this case was perhaps influenced by the fact that her then 4-year-old brother had congenital amblyopia of both eyes, without demonstrable fundus changes.

Before ending the account of the material, we may return for a moment to the group of cases of optic nerve atrophy listed in column (5) of Table 1 (p. 13). During the 1897 to 1948 period, 31 such cases were admitted; 9 of them are included in the present material. These were of the secondary retinitic type. Since many of the cases of retinochoroiditis — and, with a sufficiently long observation period, perhaps most of them — seem to exhibit apparently secondary atrophy of the discs, there is reason to make a closer study of the whole group listed in this column.

Of the remaining 22 cases in column (5), the following six, TI 335, 362, 570, 768, 1339 and 1350, belong to altogether five families with probably genetically-conditioned optic atrophy, dominant in two families and recessive in three. In every case, the atrophy did not seem to be of retinitic type, but of the primary type, with pure white discs and no other fundus changes. In two of the recessive families, all the affected persons also suffered from epilepsy and organic neurological manifestations. The occurrence of these cases may give some idea of the frequency of genetically determined congenital optic nerve atrophy.

In five cases, *i. e.*, TI 332, 431, 577, 916 and 1177, there was a probable association with meningoencephalitis in the first year of life. In one case, TI jmh, bitemporal optic nerve atrophy was combined with obesity and hypogenitalism of uncertain origin, probably congenital syphilis. In three cases, *i. e.*, TI 1073, 1169 and 1342, marked oxycephaly or hydrocephalus was present in addition to optic nerve atrophy. In one case, TI 363, there was optic nerve atrophy in one eye and atrophy of the eyeball in the other.

We now compare columns (5) and (6) in Table 1 on page 13. It is evident that the diagnosis optic nerve atrophy is relatively less frequent

than the diagnosis retinochoroiditis. The early period, 1899—1903 is an exception; there being 13 cases of optic nerve atrophy and 7 of retinochoroiditis. Of the cases then denoted as optic nerve atrophy, five proved to be secondary cases in the proband families. The remaining eight cases in the 1899—1903 period are distributed as follows. TI 332, 335, 362 and 363 have already been accounted for. In two cases, TI 337 and 352, ophthalmologic case records are lacking; the patients were born in 1886 and 1887, respectively. Only scanty data exist for two other cases, TI 325 and 336, born respectively in 1887 and 1888. The latter had a brother who was blind from birth and who died at the age of five. Obviously, some of these cases might have belonged to the group studied in the present investigation. Owing to the uncertainty of the data, they were not included.

The total material investigated consists of 105 families, of which a brief account has been given above. In these families, 15 live-born children died before the age of one year. One died at birth, and one on the day of birth. Of the remaining 13, 7 died before six months of age. They are not included in the genetical-statistical calculations, which are based on the children who survived the first year of life. Of these children, 175 exhibited blindness or impaired sight observed soon after birth or during the first year of life. Regarding F. 63 b and F. 73 b, already mentioned, see p. 42. These 175 are denoted hereafter as »the affected».

No other cases of blindness or of decreased vision were found in the sibships. They comprise an additional 303 sibs who, as far as it was possible to ascertain in the course of extensive field work, had unimpaired vision.

II

Ophthalmologic investigation

A diagnosis and ophthalmologic data were lacking for 13 out of the 175 affected. One of them (F. 93) had been a pupil at Växjö primary school, and one (F. 64) had been admitted to Tomteboda Institute in 1879. The remaining 11 had either died before reaching school age, or were older secondary cases, who died before the present investigation was made. In most cases a general physician or specialist had been consulted, but the results of the examination could not be obtained. These 11 cases are denoted as »reputed affected».

In the majority of cases, the development of the disease could be followed by means of several examinations. The intervals between them nevertheless varied greatly, as may be inferred from Table 3 and, consequently, the age at the different examinations.

An account of the examinations is given in Appendix 6 (p. 128) and a survey of these data in Table 3 (p. 26). The families are listed according to their origin in the country from north to south, and the affected members can be identified in the first column of the table. The third column shows the age at which impairment of vision was first noticed by those in charge. »0» denotes at birth or shortly afterwards and »$^1/_2$», for example, denotes at 6 months of age. The next column (4) shows the data of particular interest observed at the various examinations, the index denoting the age of the patient at the examination in question. For instance, R_{11} denotes the diagnosis »retinochoroiditis», observed at 11 years of age. The degree of vision is recorded in column (5). Reference is made to the legend to Table 3 for the meaning of the other symbols.

A closer study of Table 3 gives some idea of the development of the ophthalmologic condition and of the nature of the changes observed. It is seen that no appreciable difference exists in these respects between the families in various parts of the country.

The data in Table 3 are summarized in Table 4, which also shows the

TABLE 3. *The ophthalmological investigations in the individual cases, chronological order; based on case records in Appendix 6.*

Families registered from north to south as in Table 2.

In column (1) case numbers of the Affected in this material. Between columns (1) and (2) are given in brackets letters for families belonging to the five large pedigree complexes, the R, S, A—D, De and Su. A figure in brackets indicates relationship to the family with that number. — In column (2) are shown the schools for the blind attended by the pupils; TI=Tomteboda secondary school (›Institutet‹), Tf=Tomteboda primary school (›förskolan‹), Kr = Kristinehamn, L=Lund, Ny=Nynäshamn, Up=Uppsala, Vö=Växjö. A dash denotes that the patient has attended no school or institution for the blind. Death before reaching school age is indicated by a cross. — In column (3) is indicated P=proband and S=secondary case. Cases from the primary school registered in 1946 are denoted S(P). A dash indicates a patient not included in the present material. The figures in column (3), e. g. 0, $^1/_2$, $<^1/_2$, $^{10}/_{12}$, <1, etc. indicates the time when the impairment of sight was observed, soon after birth or during the first year of life. — In column (4) is given in chronological order the investigation results or diagnoses. R=the retinal changes described in Appendix 6, including the diagnosis ›retino-choroiditis‹ in earlier records, or retinopathy, degeneratio retinae, tapeto-retinal degeneration in later records. R_{pa}=retinitis pigmentosa atypica. A_p=amblyopia or amaurosis congenita, cases without visible retinal changes. A=atrophia nervi optici oc. amb. Ca=cataract. Ke=keratoconus. Co=corneal opacities. The small figure, e. g. R_9, indicates the age of the patient at the investigation. — In column (5) is denoted the degree of visual impairment. O=total amaurosis, P=perception of light only, hm=hand-movements, fc=fingercounting. Two values in brackets indicate different values for the two eyes at one and the same investigation. — In column (6) is indicated the investigator on the occasions given in columns (4) and (5). With few exceptions T denotes Dr Forsmark who was ophthalmologist at the Tomteboda Institute during the years 1905—1944. Since 1944 Dr Olson has been ophthalmologist at the Tomteboda. Investigations by him are denoted with O. A=investigations by Dr Alström. Patients investigated by both Alström and Olson are denoted AO or OA in the order the investigations are performed. In these cases the ophthalmological status given in Appendix 6 always are given by Dr Olson. L=investigations by Dr Lindgren. X=investigations by other doctors and at other institutions specified in Appendix 6. The symbols for the investigators are given in the same chronological order as in column (4). To the right in column (6) are shown ERG results. ERG ext.=extinguished electroretinogram, n=normal, sn=subnormal. ERG flp=flicker electroretinogram pathological, for details see Appendix 6.

Family No.	School	Observed age of impaired vision	Ophthalmological status	Degree of vision	Examinations
1	2	3	4	5	6
I a (R)	TI	P $^1/_2$	R_9 $[R + Ca]_{55}$ oper	$^1/_{60_9}$ O_{55}	T AOX ERG ext.
b	Kr	S 0	— R_{41} R_{47}	— Pfc $1m_{41}$	AX
c	—	S 0	— $[R_{pa} + Ca]_{33}$	— $[^{0.5}/_{60}—^1/_{60}]_{33}$	X
2 a (R)	Up.	S 0	— $[Ca + Ke + Co]_{56}$	— O_{56}	A

b	RI	S 0	— R_{41} R_{47}	— Pic Tm_{41}		AX	
c	—	S 0	— $[R_{pa} + Ca]_{33}$	— $[^{0.5}/_{60}—^{1}/_{60}]_{33}$		X	

2 a (R)	Up.	S 0	— $[Ca + Ke + Co]_{56}$	— O_{56}		A		
b	TI	P 0	R_{13} R_{19} $[R + Ca]_{51}$ do.$_{58}$	$[^{1.5}/_{60}]_{13}$ $P^{?}_{51}$	TT	A	X	
3 a (R)	TI	P 0	R_{12} R_{57}	$[^{1.5}/_{60} — ^{1}/_{60}]_{12}$ P_{57}	T	A		
b	—†	S 0	»reputed affected«	»vision as bad as 3a«	—			
c	—†	S 0	» »	»blind since birth«	—			
d	—†	S 0	» »	»poor sight since birth«	—			
e	—†	S 0	» »	» » » »	—			
4 a (R)	TI	P 0	R_{12} (macula) R_{19} (macula)	$[+ 9 : ^{2}/_{50} — ^{3}/_{50}]_{12}$ do.$_{19}$	TOA	O		
5 a (R)	TI	S 0	A_{11} $[A + Ca\ incip]_{16}$ $\dot{+}_{16}$	$[^{1.5}/_{60}]_{11–16}$	T	T		
6 a (R)	TI	P < 1/2	R_{15} $[R\ (macula) + Ca]_{46}$	$[[^{0.2}/_{60} — hm]_{15}$ P_{46}	T	AO		ERG ext.
7 a	TI	P 0	Ap_9 Ap_{47}	$[^{4}/_{60}]_{9}$ $(fc < 1\ m)_{47}$	T	A		
b	TI	P 0	Ap_7 $[Ca + Ke + Co]_{46}$ oper.	$[^{4}/_{60}]_{7}$ $(fc —)_{46}$	T	X		
c	—†	S 0	»reputed affected«	»blind since birth«	—			
d	TI	P 0	Ap_8 Ap_{34} $[Ap + Ca]_{44}$	$(^{2}/_{60} — ^{1}/_{60})$ $[fc < 1\ m]$ do.$_{44}$	T	A	AO	ERG ext.
8 a (S)	TI	P 0	R_8 $\dot{+}_{14}$	$(hm — P)_8$	T			
b	TI	P 0	R_7 R_{25}	$(hm — P)_7$ P_{25}	T	A		
c	TI	P 0	R_8 (macula) do.$_{18}$	$^{1}/_{60_8}$ $[^{2}/_{50} —^{4}/_{50}]_{18}$	T	OA		
9 a (S)	Tf	S 0	Ap_7 Co_{16}	P_7 O_{16}	T	X		
b	TI	P 0	R_7 R_{17} $[R + Ca + Ke + Co]_{27}$	$[O — P]_7$ O_{17} O_{27}	T	A	AO	ERG ext.
10 a (S)	TI	P 0	$[(R) + (Ke)]_8$ $[R + (Ke)]_{17}$	O_7 O_{17}	T	O		ERG ext.
[— (S)	Tf	— 0	$[Ap + (Ke)]_7$	O_7	T	O		]
11 a (S)	TI	P 0	R_{11} $[R + Ca]_{49}$	$[^{0.2}/_{60} — hm]_{11}$ $(P)_{49}$	T	AO		ERG ext.
b	TI	P 0	R_8 $[R + Ca + Ke]_{45}$	$[P — ^{1}/_{60}]_8$ $[O — (P)]_{45}$	T	AO		ERG ext.
[— (S)	—	— 0	Cataracta congenita, see p. 83	O	X	O]		

1	2	3	4	5	6
12 a (S)	TI	P 0	R_7 $[R+Ke]_{33}$	O_7 O_{33}	T A
b	L	S 0	$[Ca\ dx + A\ sin]_8$	O_8	X
13 a	TI	P 0	$[R+Ca]_9$ $[R+Ca+Co]_{43}$ do.$_{53}$	$[O - {}^2/_{60}]_9$ $[O$ — fc 1m$]_{43}$ do.$_{53}$	T A AX ERG sn, ext. flp.
14 a (D)	TI	P $^{10}/_{12}$	Ap_9 Ap_{20}	$[{}^2/_{50}]_9$ $^4/_{50_{20}}$	T AX
15 a (D)	—	S 0	— Ap_{74}	— fc 2 m	— AO ERG n, flp
b	—	S 0	— Ap_{66}	— fc 2—3 m	— A
16 a (D)	TI	P 0	Ap_9 Ap_{50} Ap_{60}	$[+3|0.1]_9$ 0.1_{50} 0.1_{60}	T A AO ERG sn, flp
17 a (D)	TI	P 0	R_7 R_{49}	$[hm]_7$ P_{49}	T AO ERG ext.
18 a (A)	TI	P 0	R_8 R_{24} $[R+Ca]_{34}$	O_8 $(P?)_{24}$ P_{34}	T A AO
19 a (A)	TI	P 0	R_{11} $\dagger_{18}$	O	T
20 a (A)	TI	S 0	(Ap_{13}) A_{14} $\dagger_{21}$	P	T
b	TI	S 0	(Ap_{11}) A_{12} $\dagger_{24}$	P	T
21 a (A)	TI	P 0	R_{12} $\dagger_{17}$	$[{}^3/_{60} - {}^1/_{60}]_{12}$	T
22 a (A)	(Hä-) L	S 0	$(R+A)_{11}$ $\dagger_{16}$	$fc?_{11}$	X
b	Kr	S 0	Rpa_{12} R_{29}	$0.1 - < {}^1/_{60}]_{12}$ $[P?]_{29}$	X A
c	Kr	S 0	Rpa_{14} R_{25} $[R+Ke+Co]_{34}$	$[{}^3/_{60} - {}^1/_{60}]_{14}$ P_{25} P_{34}	X A AO ERG ext
23 a (A)	TI	P 0	R_{13} $[R+Ca+Ke]_{54}$	$[P - {}^{0.1}/_{60}]_{13}$ $[P?]_{54}$	T A
24 a	TI	P < $^1/_2$	Ap_9 Ap_{17}	$[0.1]_9$ $[0.1 - {}^3/_{50}]_{17}$	T OA
25 a	TI	P 0	Ap_7 do.$_{10}$ $[Ap+Ke+Co]_{18}$	$[{}^{0.2}/_{60} - {}^{0.1}/_{60}]_7$ do.$_{18}$	TT OA
b	TI	P 0	Ap_5 $(R)_7$ Ap_{18}	P_5 hm_7 do.$_{18}$	XT OA
26 a	TI	P 0	R_7 R_{15} $[R+Ke+Co]_{33}$	$[{}^{0.6}/_{60}]_7$ $[{}^{0.25}/_{60}]_{15}$ hm_{33}	T T AO ERG ext.
b	TI	P 0	R_6 R_{17} (macula)	$[{}^1/_{60}]_6$ hm_{17}	T T
27 a	TI	P < $^1/_3$	Ap_8 $(Ap+Ke)_{12}$ $[Ap+Ke+Co]_{20}$ do.$_{35}$	$[{}^1/_{60} - P]_8$ fc 1 m_{12-20} $^1/_{50_{35}}$	T T T AO

b	TI	P 0	R_6 R_{17} (macula)	$[^1/_{60}]_6$ hm_{17}	T T	

27 a	TI	P < 1/3	Ap_8 $(Ap+Ke)_{12}$ $[Ap+Ke+Co]_{20}$ $do._{35}$	$[^1/_{60} - P]_8$ fc 1 m_{12-20} $^1/_{50 35}$	T T T AO	
28 a	Tf (TI)	S (P) 1/2	Ap_2 $do._4$ $do._7$ B_8 R_{16}	[not fc]$_4$ hm_{8-16}	X X T OA O	
b	—	S < 1/3	$R^7/_{12}$ R_7	$[P?]^7/_{12}$ hm_7	X O ERG ext.	
29 a	TI	P 0	R_9 (macula) $[R+Ca]_{45}$ (macula)	$[+3 \mid {}^2/_{60}]_9$ P_{45}	X AO ERG ext.	
30 a	TI	P < 1	R_{13} R_{51}	$^4/_{60}$ $[>P - fc\ 1\ m?]_{51}$	T A	
31 a	TI	S 1/2	A_{14} Ca_{55}	O_{14} O_{55}	T A	
b	TI	P 0	R_9 (macula) $\dagger_{10}$	O_9	T	
32 a (De)	—	S 0	— R_{35}	— $[^1/_{50}?]_{35}$	— A	
b	—	S 0	»reputed affected»	— (P_{31})	— —	
33 a (De)	Up.Ny.Võ	S 0	— R_{52} $[R+Ca]_{62}$ (macula)	— P_{53} hm_{62}	— A AO ERG ext.	
b	—	S 0	— R_{48} $[R+Ca]_{58}$	— P_{48} $[hm - fc]_{58}$	— A AO ERG ext.	
c	—	S 0	»reputed affected» $\dagger_{30}$	—	—	
d	TI	P 0	R_8 $\dagger_{32}$	$[^2/_{60} - {}^3/_{60}]_8$	T	
34 a (De) son of 33 b	TI	P 0	R_7 R_{15} R_{25}	$[0.1 - {}^4/_{50}]_7$ $[fc < 1\ m]_{25}$	T OA AO ERG ext.	
35 a	Tf	S(P) 0	Ap_9 A_{17}	$[hm - {}^1/_{50}]_9$ $[^{0.5}/_{60} - {}^1/_{60}]_{17}$	TOA X	
36 a	TI	P 0	$(R)_8$ R_{17} R_{20} $(R+Ca)_{30}$	$[0.1]_8$ $[^1/_{50}]_{17}$ $[hm - fc\ 1\ m]_{30}$	T T L AO ERG ext.	
b	TI	P 0	Ap_7 $do._{12}$ $(R)_{16}$	$[^1/_{60}]_7$ $do._{12}$ $do._{16}$	T OA O	
37 a	Tf	S(P) 0	A_7 Ap_9	$[0.1 - 0.2]_{7-9}$	T OA	
38 a (Su)	TI	P 0	R_9 R_{16} R_{21} $[R+Ke+Co]_{31}$	hm_9 P_{21} $[O - P?]_{31}$	T T A AO ERG ext.	
39 a (Su)	TI	P 0	Ap_1 (Ap_7) R_9 R_{17}	— O_{7-9} O_{17}	X T OA O	
40 a (Su)	TI	P < 1	$[R+(Ca)]_7$ $[R+(Ca+Ke)]_{17}$ $[R+Ca+Ke+(Co)]_{39}$	O_7 O_{39}	T T AO ERG ext.	
41 a (Su)	TI	S 0	A_9 $\dagger_{49}$	P?	T	
b	TI	S 0	A_{12} Ke_{54} $[Ke+Co+Ca]_{63}$	$[P - {}^{0.1}/_{60}]_{12}$ O_{54} P_{63}	T X AO	

1	2	3	4	5	6
42 a	TI	P 0	(Ap_3) R_7 R_{18} $[R+Ke]_{24}$ $[R+Ke+(Co)]_{33}$	$[O?]_3$ O_7 O_{24} $[O-P?]_{33}$	X T T L AO ERG ext.
b	TI	P 0	R_7 R_{14} R_{18}	O_7 do.$_{18}$	T OA O
43 a	TI	S 0	A_7 $[R+Ca]_{50}$ $[R+Ca]_{59}$	O_7 O_{59}	T L AO
b	TI	P 0	R_7 R_{21} $[R+Ke+Co]_{53}$	O_7 O_{53}	T X AO
44 a	TI	P 0	R_{11} R_{16} $[R+Ca]_{29}$ $[R+Ca+Ke+Co]_{38}$	$[^2/_{60}]_7$ $[hm-P]_{16}$ P_{29} P_{38}	T T L AO ERG ext.
b	TI	P < 1	R_7 R_{17} R_{24} $[R+(Ca)+(Ke)]_{33}$	$[^1/_{60}-{}^{0.5}/_{60}]_7$ $[hm-P]_{33}$	T T L AO ERG ext.
45 a	TI	P 0	Ap_{11}	$[^2/_{60}]_{11}$	T
46 a	TI	P 0	R_{10} $[R+Ca+(Ke)]_{62}$	P_{10} O_{62}	T O
b	TI	P 0	R_9 $[R+Ca]_{61}$ oper.	P_9 P_{61}	T AOX ERG ext.
47 a	Tf	S 0	A_7 †$_8$	O_7	T
b	—†	S 0	»reputed affected»	»blind as the sibs»	—
c	TI	P 0	(R_2) Ap_7 Ap_{32}	O_2 O_7 O_{32}	X T AO ERC ext.
48 a	TI	S 0	A_{13} R_{25}	P P	T X
b	TI	P 0	R_{12} †$_{12}$	$[^1/_{60}-{}^{0.5}/_{60}]_{12}$	T
c	TI	P 0	R_8 $[R+Ca]_{48}$	$[^{0.5}/_{60}-P]_8$ O_{48}	T AO ERG ext.
49 a	TI	P 0	$(R)<_1$ R_7 $[R+Ke+Co]_{33}$	— O_7 P_{33}	XT AO ERG ext.
50 a (85)	TI	P 0	Ap_{11} Ap_{33}	$[0.1]_{11}$ $[-3 \mid 0.2-0.1]_{33}$	T AO ERG n, flp
51 a (!)	TI	P 0	R_{10} $[R+(Ca)]_{18}$ $[R+Ca]_{38}$	$[0.1-{}^4/_{60}]_{10}$ $[^1/_{60}]_{18}$ P_{38}	T T AO
52 a (101)	TI	P 0	Ap_7 $[R+(Ca)]_{14}$	O_7 do.$_{14}$	T OA
53 a	TI	P < 1/3	Ap_{12} Ke_{27} $[R+Ke+Co]_{37}$	O_{12} O_{27} O_{37}	T A AO ERG ext.
54 a (55)	—	S 0	Ap_{12-27} Ap_{30}	$[-7 \mid fc\ 3\ m]_{12}$ $[-7 \mid 0.1]_{27}$ $[-6 \mid 0.1]_{30}$	X—X AO ERG sn
b	—	S 0	Ap_7 Ap_{12} Ap_{18}	$[fc\ ^1/_2\ m \mid fc\ 3.5\ m]_{7-}$ $[0.2]_{18}$	X—X
c	—	S 0	Ap_1 Ap_5 $[Ap+(Ca)]_9$	$(?)_1$ $[0.4$ at $1.5\ m]_5$ $[+1 \mid 0.2$ at $1.5\ m]_9$	X—X—X
55 a (54)	TI	P 0	Ap_{10} Ap_{16} Ap_{23}	$[+2 \mid {}^3/_{50}]_{10}$ $[+3 \mid {}^3/_{50}]_{15}$ do.$_{23}$	T OA AO ERG (nystagmus)

			Ap_7	Ap_{12}	Ap_{18}	$[fc\ ^1/_2\ m \mid fc\ 3.5\ m]_7 - [0.2]_{18}$	X—X
c	—	S 0	Ap_1	Ap_5	$[Ap + (Ca)]_9$	$(?)_1\,[0.4\ at\ 1.5\ m]_5\,[+1 \mid 0.2\ at\ 1.5\ m]_9$	X—X—X

55 a (54)	TI	P 0	Ap_{10}	Ap_{15}	Ap_{23}	$[+2 \mid {}^2/_{50}]_{10}$	$[+3 \mid {}^3/_{50}]_{15}$	$do._{23}$	T OA AO ERG (nystagmus)
56 a	TI	P < 1/2	R_{13}	R_{42}	.	$[^{2.5}/_{50}]_{13}$	$[^1/_{50?}]_{42}$		T A
57 a	TI	P 0	Ap_{12}	$[Ap+(Ke+Ca)]_{14}$	$[Ap+Ke]_{34}$ $[R+Ke]_{44}$	P_{12}	$do._{14}$	$do._{34}$ $do._{44}$	T T A AO ERG ext.
58 a	TI	P < 1	$[R + (Ca)]_{11}$	$[R + (Ca) + Ke]_{16}$		O_{11}			X T T
59 a	TI	P 0	$[R + (Ca)]_9$	$do._{17}$		O_9	O_{17}		T OA O
60 a	TI	P < 1	R_{12}			hm_{12}			T
b	TI	P < 1	R_{13}	R_{37}		$[^1/_{60}]_{13}$	P_{37}		T AO ERG ext.
61 a	TI	P 0	R_{12}			P			T
b	TI	P 0	R_{12}	R_{35}	$[R + Ca + (Ke?)]_{45}$	O_{12}	O_{35}	O_{45}	T L AO ERG ext.
62 a	— †	S 0	»reputed affected»			»blind»			—
b	TI	P 0	R_{13}	$[R + Ca + Ke]_{50}$		O_{13}	O_{50}		T O
63 a	TI	P < 1	R_{12}	R_{30}	$[R + Ca]_{40}$	$[hm - {}^{0.1}/_{60}]_{12}$	P_{30}	P_{40}	T L AO ERG ext.
b	TI	S < 1	R_{12}	R_{28}	R_{38}	P_{12}	P_{28}	P_{38}	T L AO ERG ext.
c	TI	P 0	R_{10}	R_{26}	R_{36}	hm_{10}	P_{26}	P_{36}	T L AO ERG ext.
64 a (65)	TI	S 0	»no diagnosis»			»blind»			T
65 a (64)	L	S 1/2	»retinal disease» 1/2	A_{13}	$\dagger_{24}$	—	O_{13}		X X
b	TI	P 0	R_{12}	$[R + Ke + (Co) + (Ca)]_{38}$		O_{12}	O_{38}		T AO ERG ext.
66 a	Tf	S(P) < 1/4	R_6			O_6			T
67 a	TI	P < 1	$(R)_7$	$do._{16}$	$[Ke + Co + Ca]_{27}$	$[^{0.1}/_{60}]_7$	$do._{16}$	(fc 1 m)$_{27}$	T T AO ERG ext.
68 a	Võ	S 0	$(R?)_7$	$\dagger_{19}$		O_7			X
b	TI	P 0	R_{12}	R_{37}	$(R + Ke)_{47}$	O_{12}	O_{37}	O_{47}	T A AO ERG ext.
69 a (70)	TI	P 0	$[R+(Ca)]_7$	$[R+Ca]_{14}$	$[R+Ca+Ke+Co]_{29}$	O_7	O_{14}	$(P)_{29}$	T T O
b	TI	P < 1/2	R_7	$do._{14}$	$do._{16}$	O_7	O_{14}	O_{16}	T OA O
70 a (69)	TI	S 0	A_{12}	$\dagger_{25}$		»blind since birth»			T
b	—	S 0	»reputed affected»	$\dagger_7$		»	»	»	—

1	2	3	4	5	6
71 a	TI	P $<$ 1/2	Ap_{14} $[R + (Ca)]_{54}$	hm_{14} O_{54}	T AO ERG ext.
72 a	TI	P $<$ 1/2	R_{14}	P_{14}	T
73 a	TI	P $<$ 1/2	R_{10} R_{17} R_{29}	$[+4 \mid 0.1]_{10}$ do.$_{17}$ $[<1/100]_{29}$	T T AO ERG ext.
b	TI	S 0	R_8 R_{17} R_{27}	$[+7 \mid 0.1 - 2.5/50]_8$ $[+7 \mid 0.4 - 0.2]_{17}$ $[+7 \mid 4/50 - 0.1]_{27}$	T T AO ERG ext.
74 a	TI	P 1/2	Ap_8 $[(Ca) + (R?)]_{12}$ do.$_{17}$	P_8 P_{12} P_{17}	T T T
75 a	TI	P 1/2	R_7 R_{44}	O_7 O_{44}	T AO ERG ext.
76 a	TI	P 1/2	$[R + Ca]_7$ $[R + Ca + Ke]_{49}$	O_7 O_{49}	T AO ERG ext.
b	TI	S 0	Ca_7 $[Ca + Ke + Co]_{47}$	O_7 O_{47}	T A
c	Tf	S 0	R_7 R_{13} $[R+Ke+Co]_{18}$ $[R+Ke+Co]_{36}$	O_7 O_{13} O_{18} O_{36}	T X X X
77 a	TI	P 0	Ap_{13} Ap_{17} Ap_{22} Ap_{28}	$[0.1]_{13}$ do.$_{17}$ $[0.1 - hm]_{22}$ do.$_{28}$	T T L—X X
78 a	TI	P 0	R_{13}	$[5/60 - 0.1]_{13}$	T
79 a	TI	P 0	R_{13} R_{18} R_{43} $[R + Ca]_{52}$	— P_{18} P_{43} P_{52}	T T L AO ERG ext.
b	TI	P 0	R_{13} R_{17} R_{33}	$[P - hm]_{13-17}$ P_{33}	T T L
80 a (81)	TI	P 0	$[Ap + (Co) + (Ca)]_7$ do.$_{10}$ do.$_{15}$ $[Ap + + Ca + Ke]_{20}$	O_{7-15} O_{20}	T OA O AO ERG ext.
81 a (80)	TI	P 0	R_{12} $[R + (Ca)]_{57}$	$[hm]_{12}$ P_{57}	T AO ERG ext.
b	TI	P 0	R_{11} R_{23} R_{45}	— — —	T X X ERG ext.
c	TI	P 0	R_7 R_{17}	P_7 P_{17}	T T
82 a	TI	P 0	Ap_7 Ap_9 Ap_{16}	$[P - hm]_7$ do.$_9$ do.$_{16}$	T OA O
83 a	TI	P 0	R_8 R_{13} R_{20} $[R + Ca]_{28}$	$- [0.2 - 2.5/60]_{13}$ $[P - 3/50]_{20}$ O_{28}	X T T L
84 a	TI	P $<$ 1/4	$[R + (Ca)]_{11}$ $[Ca + Ke]_{36}$ $[R + Ca + + Ke + (Co)]_{46}$	O_{11} O_{36} O_{46}	T A AO ERG ext.
85 a (50)	TI	S 0	Ca_8 oper. $(A)_{15}$ »small atroph. bulbi»$_{46}$	O_8 O_{15} O_{46}	T T L
b	TI	P 0	$[R + Ca]_{11}$ $[R + Ca + Ke + (Co)]_{48}$	$[O - P]_{11}$ $[»O» - O]_{48}$	T AO ERG ext.
86 a	TI	P $<$ 1/4	Ap_7 $[Ap + Ke + (Co)]_9$ $[R + Ke + Co]_{10}$ do.$_{17}$	O_7 O_{9-10} O_{17}	T T OA O

85 a (50)	TI	S 0	$Ca_{8\ oper.}$ $(A)_{15}$ »small atroph. bulbi»$_{46}$	O_8 O_{15} O_{46}	T T L	
b	TI	P 0	$[R + Ca]_{11}$ $[R + Ca + Ke + (Co)]_{48}$	$[O - P]_{11}$ $[»O» - O]_{48}$	T AO	ERG ext.

86 a	TI	P $< 1/4$	Ap_7 $[Ap + Ke + (Co)]_9$ $[R + Ke + Co]_{10}$ $do._{17}$	O_7 O_{9-10} O_{17}	T T OA O	
b	L	S 0	$[Ke + atrophia\ bulbi]_7$ $[do. + A]_9$	$O \mid O_7$ O_9	X | A X	
87 a	TI	P 0	R_{10} $[R + (Ca)]_{17}$ $[R + Ca]_{42}$	P_{10} P_{17} O_{42}	T T AO	ERG ext.
b	TI	P 0	$—_9$ R_{14-19} $[R + Ca]_{38}$	$[< 1/60]$ P_{14-19} P_{38}	X T AO	ERG ext.
c	TI	P 0	R_{12} $[R + Ca]_{35}$ (macula)	P_{12} P_{35}	T AO	ERG ext.
88 a	TI	P 0	$[R + Ca]_6$ $[R + Ca + (Ke)]_8$ $[R + Ca + Ke]_{15}$	P_{6-8} P_{15}	T OA O	
89 a	TI	P 0	Ap_8 $do._{10}$ $do._{12-13}$ $do._{17}$	$[1.5/60—hm]_{8-17}$	T T OA O	
90 a	—†	S 0	»reputed affected»	»blind since birth»	—	
b	TI	P 0	R_{12} $do._{19}$ $(R?)_{28}$	$[4/60—3/60]_{12}$ $[3/60—2/60]_{19}$ P_{28}	T T X	
91 a	TI	S(P) 0	A_7 A_{11} A_{13} $†_{13}$	$O_{7-11-13}$	T OA O	
b	(TI)	S 0	Ap_{9-14} $[Ap + (Ke)]_{15}$	$P_{9-14-15}$	O—O O	ERG ext.
92 a	TI	P 0	Ap_{11-12} Ap_{19}	$[2/50]_{11}$ $do._{12}$ $do._{19}$	T OA O	
b	TI	P 0	Ap_9 $(R)_{10}$ (macula) $do._{15}$ $do._{19}$	$[3/100]_9$ $do._{10}$ $[2/50]_{15}$ $do._{19}$	T OA O O	
93 a	Vö	S 0	— $†_9$	»blind since birth»	X	
b	TI	P 0	$[Ap + (Ca)]_{11}$ $do._{16}$ $do._{34}$	P_{11} P_{16} P_{34}	T T AO	ERG ext.
94 a	Kr	S 0	— $[R + Ca]_{71}$	— O_{71}	— AO	ERG ext.
b	Vö	S 0	$—_9$ $[R + Ca]_{68}$	— $[P — O]_{68}$	X AO	
c	TI	S 0	A_8 $†_{31}$	$[2/60—1.5/60]$	T	
d	TI	P 0	R_{12} $do._{15}$ R_{56}	$[1.5/60—4/60]_{12}$ $[O—hm]_{56}$	T T O	
95 a	L	S < 1	$[A + Ca + (R?)]_{11}$ $do._{26}$	$—_{11}$ $—_{26}$	X X	
b	TI	P 1/2	R_7 R_{11} R_{16}	O_7 O_{11} O_{16}	T OA O	
96 a	TI	P < 1	R_7 R_{14} (macula) R_{17}	P_7 — —	T OA O	
97 a	TI	P 0	R_{11} $[Co + A?]_{25}$ $†_{25}$	O_{11} O_{25}	T X	
98 a	TI	P 0	R_{15} R_{42}	$[0.2/60]_{15}$ P_{42}	T X	
99 a	TI	P < 1	Ap_{10} Ap_{16} Ap_{18}	$[4/50]_{10}$ $—_{16}$ $[0.1]_{18}$	T OA O	

1	2	3	4	5	6
100 a	Tl	P 0	Ap_{12} R_{20} R_{43}	$[^1/_{60}]_{12}$ do.$_{20}$ $[^1/_{50}]_{43}$	T T AO ERG ext.
b	Tl	P 0	Ap_{11} $(R?)_{15}$ Ap_{38}	$[^1/_{50}]_{11}$ $[^2/_{60}]_{15}$ $[^1/_{50}]_{38}$	T T AO ERG ext.
101 a (52)	Tl	P 0	Ap_8 $[Ap+(Ke)+(Co)]_{14}$ do.$_{16}$ $[Ap+$ $+Ke+Co]_{18}$	$[hm]_8$ $[hm]_{14}$ —$_{16}$ —$_{18}$	T T OA O
102 a	Tl	P 0	R_{12} $[R+Ca+Ke+(Co)]_{47}$	P_{12} O_{45}	T AO ERG ext.
b	Tl	P 0	$[R+Ca]_{11}$ $[R+Ca+Ke]_{43}$	hm_{11} P_{43}	T AO ERG ext.
c	Vö, L	S 0	R_{11} R_{31}	O —$_{31}$	X X
103 a	Tl	P 0	R_{13} $[R+CA+Ke]_{42}$ $[R+Ca+Ke+Co]_{52}$	P_{13} P_{42} P_{52}	T L AO ERG ext.
104 a	Tf (Tl)	S(P) 0	Ap_7 Ap_8 $[Ap+Ke]_{15}$	O_7 do.$_{15}$	T OA O
105 a	Tl	P $^1/_4$	R_7 $[R+Ke+Co]_{50}$	O_7 $(P)_{50}$	T O
b	Tl	P 0	R_{12} R_{17} R_{45}	hm_{12} P_{17} P_{45}	T X AO ERG ext.

The pupillary reaction to light was often hard to judge because of the involuntary eye-movements. However, it was negative in cases with total amaurosis, positive in cases with some residual vision, and in cases with perception of light only most often a weak reaction.

TABLE 4. *Survey of the ophthalmological investigations. Summary of column (4) in Table 3.*

Columns (2)—(4) show results of the earliest examinations (under 15 years of age). In (5) are given the numbers of (2) who were reexamined later. Columns (6)—(12) show results of the most recent investigations of these patients. — Under (6) are given cases of retino- choroiditis without complications; in brackets, cases of retino-choroiditis with cataract or keratoconus, also given in (12). R=retino-choroiditis, Ap=amblyopia et amaurosis congenita, A=atrophia n. opt., Ca=cataract, Ke=keratoconus.

(1) Diagnosis	(2) No.	(3) With Ca	(4) With Ke	(5) No. investigated later	(6) R	(7) Ap	(8) A	(9) Ca	(10) Ke	(11) Ca + Ke	(12) R + Ca/Ke
R	93	11	1	79	29(+ 50)	·	·	21	10	19	50
Ap	43	2	1	40	6(+ 7)	16	1	3 + 3(R)	5 + 4(R)	2	7
A	15	1	1	6	1(+ 1)	—	1	2 + 1(R)	—	1	1
Ca	2	2	—	2	—	—	(1)[1]	(1)[1]	—	1	·
Not examined	23	·	·	10	3(+ 5)	1[1]	—	0 + 5(R)	—	1	5
Σ	175 (176)	16	3	137	39(+ 63)	17	2	36	19	24	63

[1] Atrophia bulbi.

development from the first observation until the last. It must be borne in mind that conclusions can only be drawn with caution. This is because the observation period is relatively short in some cases, and even in the others is of greatly varying length. Only a long observation period can determine the extent to which the condition will remain stationary — which seems to apply in some cases — or the frequency of the subsequent appearance either of such complications as cataract or keratoconus, or of visible fundus changes which may or may not be progressive. In view of this fact, the frequencies recorded in Table 4 are presumably to be regarded as minimum figures.

With due reservation for the varying length of the observation period, it may nevertheless be of interest to study the schematic survey in Table 4 and to consider the frequencies found in it.

Of the 93 patients in whom retinochoroiditis was diagnosed at the first examination, 79 underwent a later examination. Complications were then present in 50 of them (63 per cent), consisting in 40 cases of cataract. Of these patients 11 had had cataract or incipient cataract at the first examination; there were thus 29 new cases. In 29 cases, keratoconus with or without corneal opacities had appeared; in 19 cases there was concomitant cataract.

In 43 cases with the diagnosis Ap, no fundus changes were present initially; in 1 of them there was keratoconus, and in 2 cataract which did not prevent inspection of the fundus. A later examination was made in 40 cases. In 13 of these cases (33 per cent) retinochoroiditis was then observed, with additional complications in 7 of them. Cataract preventing inspection of the fundus had developed in 5 cases; in 2 of them there was coincident keratoconus with or without corneal opacities. In 16 of the cases re-examined, *i. e.*, 40 per cent, no additional lesions of the fundi were observed. It must, however, be recalled that the observation period was fairly short in these patients, most of whom were young. Thus, altogether 8 of the Ap patients who underwent re-examination exhibited cataract.

Of the 15 cases with the diagnosis bilateral optic nerve atrophy, one of them with concomitant incipient cataract, 6 were re-examined. Two of them then exhibited retinochoroiditis, in one case with cataract as well. Cataract preventing inspection of the fundus had developed in 3 cases, in one of them with coincident keratoconus.

Early cataract preventing inspection of the fundus was observed in two secondary cases at 9 years of age; operation was performed on one of them (F. 85 a), revealing a somewhat pale and blurred disc.

TABLE 5. ***Survey of the ophthalmological investigations, by age group, absolute numbers. Summary of section (4) in Table 3.***

Each patient counted once only in each age group, but may occur in more than one age group. Figures without brackets show results of the earliest, and figures in brackets of the most recent examinations at each age; where only one examination was made, this is included in both figures.

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
	Age <15	Number of (2) with			Age 15—45	Number of (6) with			Age 45—ω	Number of (10) with		
		Ca	Ke	Ca/Ke		Ca	Ke	Ca/Ke		Ca	Ke	Ca/Ke
R	93	11(11)	1(2)	—(1)	76	9(16)	8(11)	8(12)	34	14(16)	3(3)	8(8)
Ap	43	2(5)	1(6)	—(1)	23	1(1)	5(5)	1(1)	2	—	—	—
A	15	1(1)	1(1)	—	2	1(1)	—	—	—	—	—	—
Ca	2	2(2)	—	—	—	—	—	—	6	2(2)	—	4(4)
Σ	153	16(19)	3(9)	—(2)	101	11(18)	13(16)	9(13)	42	16(18)	3(3)	12(12)

No improvement in vision resulted. Both patients were re-examined almost 40 years later. In the operated case, atrophy of the eyeballs had developed. This had not occurred in the other case, but marked keratoconus was present, as well as extensive, dense, milky opacities of the cornea. Both patients had sibs with »retinochoroiditis».

Of the 23 cases with no known examination when of school age (actually, 21 cases, *cf.* p. 25), 10 were examined later. Eight of them then exhibited retinochoroidal changes, in five cases with coincident cataract. In an additional case, inspection of the fundi was impossible, owing to the presence of cataract, keratoconus and corneal opacities.

The above account, together with a study of Table 3, should give some conception of the development in the individual cases. It must, however, once again be stressed that the length of the observation period varies greatly. Many of the patients are still young and have therefore been under observation for only a short period, whereas other, older patients died before re-examination. Consequently, the frequency figures based on Table 4 presumably give only minimum figures for the possible occurrence of complications.

A more accurate idea of the probable development should therefore be obtained from Tables 5 and 6, in which the observations made at different ages have been assembled. See further the text of the tables. In those cases in which retinochoroidal changes had been observed on some occasion, these are recorded in the Table as R cases, even if inspection had subsequently been prevented by the development of opacities of the media.

TABLE 6. *Survey of the ophthalmological investigations, by age group, percentages. Distribution in per cent within each age group of data given in table 5.*

For explanation of figures within and without brackets see table 5.

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
	Age < 15	Per cent of (2) with		Age 15—45	Per cent of (5) with		Age 45—ω	Per cent of (8) with	
		Ca	Ke		Ca	Ke		Ca	Ke
R	61	12(13)	1(3)	75	22(37)	21(30)	81	65(71)	32(32)
Ap	28	5(14)	2(16)	23	9(9)	26(26)	5	— —	— —
A	10	7(7)	7(7)	2	· ·	— —	—	— —	— —
Ca	1	· ·	— —	—	— —	— —	14	· ·	67(—)
	100	10(14)	2(7)	100	20(31)	22(29)	100	67(71)	36(36)

The frequency of retinochoroidal lesions is found to rise from 61 per cent in the age group under 15 years to 75 per cent in that of 15—45 years (Table 6), and to 81 per cent in the age group over 45 years. It is not unreasonable to presume that such changes are actually present at least in some of the cases with cataract preventing inspection, although they have not been observed earlier. It can also be recalled that in 71 per cent of the patients with »retinochoroiditis» in this age group cataract had developed, often making inspection impossible. For example, Case 1 a was found at examinations between 9 and 16 years of age to have retinochoroiditis but no cataract. A follow-up examination at the age of 55 showed dense, bilateral cataract, entirely preventing inspection. After operation at the Eye Clinic of Karolinska Sjukhuset, the inveterate retinochoroidal lesions could be seen.

The frequency of cases in which fundus changes were absent, *i. e.*, with the diagnosis of amblyopia or congenital amaurosis, decreases with rising age. Thus, it is about 30 per cent before 15 years of age, and about 20 per cent in the 15—45 year age group. All but two of the 42 cases observed after 45 years of age showed positive findings: »retinochoroiditis» with or without cataract, or with or without keratoconus.

With regard to the progression of the condition in the re-examined patients with bilateral optic nerve atrophy, reference is made to the data given on page 36. In most of the cases with retinochoroiditis, there was some atrophy of the discs of secondary type. This change, sometimes — or most often — combined with moderate narrowing of the vessels was found in the youngest age groups as well. In the patients examined at over 45 years of age, it did not occur in isolation.

In the youngest age group, there are two secondary cases of cataract preventing inspection of the fundus (F. 76 b and 85 a), the latter being the patient operated on at 9 years of age. Pale, blurred discs then became visible. Both patients had sibs with retinochoroidal lesions. In the oldest age group, those observed after 45 years of age, cataract was present in 14 per cent which, however, amounts to only 6 cases. If a calculation is made of the frequency of cataract, irrespective of whether or not other lesions were present or had been observed (see Table 6, below), the following is found. In the youngest age group, cataract or incipient cataract is present in 10 (14) per cent. At 15—45 years of age cataract has developed in about 30 per cent, and over 45 years in about 70 per cent.

Keratoconus was observed in 2 per cent of the cases in the youngest age group. It has developed in about 30 per cent of the 15—45 year

group. After 45 years of age, keratoconus was present in somewhat more than one-third of the cases.

In one patient in the youngest age group, F. 86 b, moderate atrophy of both eyeballs, optic nerve atrophy of both eyes and marked keratoconus were present already at 9 years of age. In the previously mentioned case F. 85 a, no such changes were present during observation up to the 18th year, but at examination when he was 46 years old, moderate atrophy of both eyeballs was found. These two cases are the only ones in the whole material in which atrophy was present. There were two cases with some retraction of the eyeballs, but no atrophy.

The degree of vision estimated at the different examinations is shown in the third column of Table 3. A survey is given in Table 7, in which

TABLE 7. *Survey of the visual acuity, absolute numbers. Summary of column (5) in Table 3. Degree of visual impairment.*

Column (2) shows results of the earliest examinations (under 15), columns (4)—(8) the results of the most recent examinations of each group of (2).

(1)	(2) No.	(3) %	(4) 0	(5) P	(6) hm 0.1/60	(7) fc 1/60	(8) 0.1—	(9) Not estimated later
0	42	28	33					9
P	29	19	6	18				5
hm 0,1/60	25	17	2	12	7			4
fc 1/60	37	25	1	8	8	15		5
0,1 —	16	11	1	2	2	1	7	3
Not estimated	27	·	2	2	2	5	—	16
Σ	176		45	42	19	21	7	
		%	34	31	14	16	5	

the material is divided into five classes. The greatest decrease in vision corresponds to total blindness, and the smallest decrease to S=0.1 or more. The individual values are recorded in Table 3.

A statement of the degree of vision existed for 149 of the patients examined at an earlier age. Total blindness was present in 28 per cent of these cases, and perception of light in 19 per cent. Vision roughly estimated to correspond to perception of hand movements, or tested visual acuity corresponding to about 0.1/60, was present in 17 per cent. The class corresponding to vision of one or a few sixtieths or fiftieths comprised 25 per cent (for details, see Table 3). In 11 per cent, there was

visual acuity of 0.1 or more. — These figures are recorded in the first column of Table 7.

Table 7 is constructed in such a way that the distribution of the first examinations is shown vertically in its left section. In the right section of the table, the distribution of the subsequent observations according to the various degrees of vision of the original classes is given horizontally. For example, 6 of those in class »P» showed progression to total amaurosis. Five patients were not re-examined.

If the respective columns are added, we obtain the distribution of vision among the different classes at the latest examination. A distinct decline is then found to have taken place; 34 per cent exhibited total blindness and 31 per cent perception of light only. Vision corresponding to perception of hand movements, or about 0.1/60, is present in 14 per cent, and vision of 1/60 or somewhat more in 16 per cent. The group representing vision of 0.1 and above amounts to 5 per cent.

When discussing Table 7, the same reservation must be made with regard to the age factor as in the discussion of Tables 5 and 6. Table 8

TABLE 8. *Percentage distribution of degree of visual impairment in the different age-groups.*

Degree of vision		Age-groups (years)		
		—15	15—45	45—
0	(1)	28	29	38
P	(2)	19	32	36
hm 01./60	(3)	17	14	17
fc 1/60	(4)	25	19	7
0.1—	(5)	11	6	2
Σ		100	100	100
		No. of cases in each age-group		
		149	100	42

gives the percentage distribution according to the degree of visual impairment in the different age groups. The gradual deterioration of vision, which seems to take place with increasing age, is clearly shown. In the group under 15 years, 47 per cent of the cases examined are totally blind or have perception of light only. The frequency rises to 61 per cent in the group aged 15—45 years, and in those over 45 years of age, three-quarters are totally blind or have at most perception of light.

This would perhaps not be surprising in view of the high incidence of cataract in this age group. The patient with »retinochoroiditis», F. 1 a, who has already been referred to, had visual acuity of 1/60 when young. At 55 years of age, only very uncertain perception of light could be established after operation for cataract. It can also be inferred from Table 3 that, in the older cases, there had been a decline in visual acuity that cannot be accounted for by development of opacities of the media.

After this schematic survey, we can enter into a general discussion of the observations made in these cases.

A consistent feature was blindness or greatly impaired vision detected soon after birth or during the first year of life. Two secondary cases would be the only exceptions. In one of them, F. 63 b, blindness was stated to have been observed at about three years of age. This patient belonged to a sibship with an additional two affected children, one blind from birth and the other observed to be blind before one year of age. In the other case, F. 73 b, impaired vision was stated to have been noticed at two years of age; in another affected sib, it had been observed at about six months of age. Both in the field-investigations, and during the examination of these families at the Karolinska Sjukhuset, it became quite evident that these statements were inaccurate. There was no doubt that in F. 63 b, as well as in F. 73 b, the defective vision had been observed early in the first year of life.

An almost constant feature was nystagmus-like, undulating or entirely irregular eye movements, their frequency varying greatly from case to case. They were also present in those patients with the least impaired visual acuity, the eye movements being even more frequent than in cases with poorer vision. Fixation was lacking in all the patients with residual vision. Thus, in every case there was a decrease in central vision. In none of the cases was tube vision stated to be present, as in retinitis pigmentosa. On the other hand, it was stated in a few cases that the patient had noticed some small spot in the periphery where the vision was slightly better than elsewhere. This spot could be found only by twisting and turning the head in a particular way. Even this gradually disappeared with increasing age. No sharply delimited loss of any part of the visual field could be demonstrated in any of the cases.

Attempts were made at the Eye Clinic of Karolinska Sjukhuset to photograph the fundus changes. This, however, was unsuccessful, owing to the eye movements. The degree of impairment of vision did not seem to be correlated clearly with the presence or absence of fundus changes.

It can be inferred from this account that, at any rate in a certain

number of cases, there is unquestionably a slow, successive decline in vision in the long run. Some cases seem, however, to remain stationary even for several decades.

The fundus changes consisted of so called »retinochoroiditis» of an uncharacteristic appearance. This fact may explain why the disease has not been identified earlier. Its final identification has been possible only by means of combined genetic studies and clinical examinations extending over long observation periods.

In young patients, there were frequently no alterations whatsoever. If any were present, they usually consisted of very small round, scarcely visible, pale spots scattered mainly in the periphery. In some cases, small round or irregular pigmented spots were also seen at this site. Alterations in the central part were seldom observed and then only sparsely. In a few cases, some of the pigment was aggregated into shapes resembling bone corpuscles, as in retinitis pigmentosa. This occurred only at some sites in the fundi; the other varieties of pigmentation were also present, and always dominated the picture. Moreover, the course and clinical features of the disease differed from those of retinitis pigmentosa. Central vision was invariably impaired and, as stated earlier, tube vision was never found. In those cases in which pigmentations resembling bone corpuscles were observed, they could be lacking in the sibs.

It is perhaps of some interest to note that in a few cases (F. 4 a, F. 8 c and F. 96 a) there was macular involvement, reminiscent of STARGARDT's recessive macular dystrophy. But the course differed from that found in this condition, nor was the lesion demonstrable in any of the affected sibs or in the other families belonging to the family complex of which two of the families form part.

In many of the cases that could be followed over a long period, progression of the fundus changes was observed; the findings are recorded in Appendix 6 (p. 128). There was distinct confluence of the pigmentations into larger foci or patches, and the central part of the fundus was affected, but seldom to the same extent as the periphery. At some sites complete atrophy of the retina and choroids developed, so that large, white areas of sclera were visible. When it could be observed, progression seems to have been particularly slow. Cases with highly defective vision to total amaurosis and inappreciable fundus changes or none at all were also observed, as can be seen from both Table 3 and Appendix 6 (p. 128). It seems as if the functional decrease appears first, and the gross anatomic fundus changes — when they do become mani-

fest — lag behind. In the young patients in which they are present, they cannot *per se* explain the severe visual defect.

Some pallor, blurring and atrophy of the discs of the so-called retinitic or secondary type, as well as narrowing of the vessels, is common especially in older cases with retinochoroidal lesions. These changes can, however, also be observed in early or young cases, in which retinochoroidal fundus changes may be lacking. Changes in the disc and the vessels, if present, do not, however, seem to be of such marked degree as in retinitis pigmentosa, in any event in such cases with a severe decrease in vision as that observed here. Opacities of the vitreous may be seen in occasional cases.

It was apparent from the earlier survey that, with rising age, cataract is an increasingly common complication, its frequency being such that it must reasonably be considered to be related to the primary disease. Incipient cataracts of both the lamellar type with riders and the polar type was found. The older cataracts were usually dense, diffuse, either unilateral or bilateral, preventing inspection of the inner eye (see, *e. g* the aforementioned case F. 1 a). Dense cataract preventing inspection is uncommon at an early age, but may occur, as stated previously.

Incipient keratoconus has been observed early in school age, but becomes more common in the later part of this period. In every case, it was bilateral. More advanced cases of keratoconus are not unusual at higher ages, and may be extremely severe. Keratomalacia is then a common finding; in some cases milky opacities of the whole cornea had developed, and made inspection impossible. As a rule, as is evident from Table 6, keratoconus is present in the older patients concomitantly with retinochoroiditis, with or without cataract. In the younger patients, on the contrary, incipient keratoconus may be present without any visible retinochoroidal changes of the fundus. Incipient, early keratoconus is presumably present in a considerably higher frequency than can be inferred from the figures at the foot of Table 6. This is because it is unlikely that particular attention was focused on this phenomenon in earlier years. Its presence, which is so common in this condition and is so rare otherwise, is naturally of great importance for a differential diagnosis.

Despite constant vigilance during the 10 years that have elapsed since the beginning of this investigation, it has not been possible to obtain any case for autopsy. However, it may be some consolation to know that the effects of post-mortem changes are usually hard to evaluate in such cases.

On the other hand, through the courtesy of Professor GÖSTA KARPE, it has been possible to examine a number of patients, altogether 62, at the electroretinographic laboratory of the Eye Clinic of Karolinska Sjukhuset. These patients represent all ages and different parts of the country, and all the large family complexes are represented by one or several cases. As may be inferred from Table 3 and Appendix 6, 92 per cent of the patients examined had extinguished electroretinograms (ERG), irrespective of whether or not retinochoroidal changes were present. In 5 cases the ERG was normal or subnormal. One was F. 50 a. This patient, with the diagnosis congenital amblyopia, had no fundus changes and relatively good vision, which seems to have remained stationary for the past 23 years. He had, in fact, the best vision of any of the affected in the material, examined at this age. The ERG of one eye was normal, and that of the other eye »probably normal». The flicker ERG however, in this case as in the other four, was pathologic. (G. KARPE.)

It might perhaps be questioned whether this case actually belongs to the disease group under investigation. However, any attempt at fixation elicited frequent, nystagmus-like eye movements, indicating a decrease in central vision. Moreover, the patient is related to F. 85, which has two affected members exhibiting a severe form of the disease, and with extinguished ERGs. The patient had been selected according to the proband definition, and the relationship was not discovered until later.

The ERG investigations in all the other cases examined, even in those with no visible fundus changes, seems to justify the inference that the hypothetical biochemical process underlying the disease involves primarily the retinal elements.

For comparison, the ERG was recorded in a patient from Tomteboda Institute with total blindness and no objective fundus changes. This case thus resembled our early cases. The patient had had normal vision until 18 months of age, when blindness occurred suddenly after acute encephalomeningitis with high fever and neuropsychiatric manifestations. Blindness was the only sequela. The child had developed normally in every other respect, and had attended the whole course at Tomteboda. Despite total blindness, the ERG in this case was entirely normal. Obviously, without the anamnestic data, it would have been difficult to determine whether or not this case had belonged to the disease group under investigation. The normal ERG together with the total loss of vision would then have been helpful.

III

Genetic-Statistical Analysis

IN the Introduction, a brief account was given of the preliminary study of the relevant cases of congenital retinochoroiditis and congenital amblyopia registered at Tomteboda Institute for the Blind. Their tendency to a familial incidence seemed to be striking, as did the increased frequency of a first-cousin relationship among the parents.

Table 2 shows a survey of the affected individuals and of their unaffected sibs belonging to the 105 families in the material. The figures apply to those who had reached at least one year of age. There are 84 affected males and 91 affected females. Of 303 unaffected sibs, 58 ± 2.9 per cent are males. In calculating the standard error, the corresponding preponderance of males (51 per cent) in the general population has been taken into account. The preponderance in the present material is hard to understand, unless it is due to chance, which might seem probable. It can, however, be recalled that a corresponding preponderance of males in the unaffected sibs, *i. e.*, 56 per cent, was present in SJÖGREN's investigation of juvenile amaurotic idiocy.

1. *Mendelian analysis*

In Table 2, the probands assembled from Tomteboda Institute, according to the definition given, are denoted in column (3) by P. They consist of the cases recorded in columns (12) and (14) of Table 1 (p. 13). The 115 probands represent 90 proband families, 10 of which are one-child families. A Mendelian analysis with WEINBERG's proband method gives 22.4 ± 2.0 per cent affected in the sibships of the proband families. The frequency figure obtained is in satisfactory agreement with the hypothesis of a monohybrid autosomal recessive mode of inheritance.

A calculation was then made with HOGBEN's a priori method (HOGBEN, 1931, 1945, 1946). This is used to calculate the expected number of

affected individuals, provided that the mode of inheritance is monohybrid autosomal recessive, with complete manifestation. HOGBEN has given a method for computing the standard error of this expected value. His method pays adequate statistical regard to the fact that only sibships with at least one affected child will be investigated. WEINBERG's proband method has, in fact, been subject to discussion on this account. It is, however, simple to carry out and merits a place as a preliminary method of estimation.

In the following tabulation, the expected and observed numbers of affected members are given for the 80 proband families, for the other 14 families, and for the whole series collectively. The 11 one-child families have been excluded from the calculations; 10 of them belong to the proband group, and 1 to the others.

	Affected Members		Standard
	Expected	Observed	Error
80 proband families	132.0	139	7.0
14 other families	24.4	25	4.2
94 families collectively	156.5	164	7.7

Thus, with HOGBEN's method as well, satisfactory agreement is found with the hypothesis of monohybrid recessivity. WEINRERG's method gives a deviation at random towards a lower figure than the expected, whereas HOGBEN's method gives a deviation tending to a higher value than the expected. Consequently, the following calculations are of interest.

HALDANE (1932) has given a method with which the true proportion of recessives may be calculated from data on small families, as is the case in human genetics. In the subsequent genetic-statistical analysis, I have used this method only, as it has certain advantages over the *a priori* methods. I quote HALDANE (1932, p. 251):

»If a group of families derived from normal parents, each family containing at least one abnormal, consists of n_s families of size s, the values of s ranging from 1 to c, and contains R recessives in all, then the most likely value of q, the proportion of normals in a family (supposed constant), is the real root other than unity of the equation

$$\frac{R}{1-q}=\sum_{s=1}^{c}\frac{s\cdot n_s}{1-q^s} \qquad (1)$$

and the standard error of q (and hence of $p=1-q$) is given by the equation

$$\sigma^{-2}=\frac{R}{q(1-q)^2}-\sum_{s=1}^{c}\frac{s^2\cdot q^{s-2}\cdot n_s}{(1-q^s)^2} \qquad (2)»$$

For proof of the theorem by application of FISHER's method of maximum likelihood, see further HALDANE (1932).

The 11 families, in which $s=1$, can be omitted, since the terms due to them cancel out. According to (1), we then get the following equation, after multiplying both sides by $(1-q)$ and inserting the values of s, n_s and R. These values have been obtained from the 94 families in the whole material with more than one child.

$$\frac{38}{1+q}+\frac{54}{1+q+q^2}+\frac{40}{1+q+q^2+q^3}+\frac{70}{1+q+..+q^4}+$$
$$+\frac{36}{1+q+..+q^5}+\frac{63}{1+q+..+q^6}+\frac{48}{1+q+..+q^7}+$$
$$+\frac{36}{1+q+..+q^8}+\frac{60}{1+q+..+q^9}+\frac{22}{1+q+..+q^{10}}=164.$$

The equation is solved by the method of trial and error, valuable help being obtained from PEARSON's Tables for Statisticians and Biometricians (Part II, Table LV, p. 258).

For $q=0.72$, the left side of the equation will be equal to 166.05, and for $q=0.73$, it will be 162.81, $\therefore q=0.726$ and $p=0.274$. According to

TABLE 9. *Calculation according to* HALDANE *of expected number of affected in sibships of different sizes, s from 2 to 11, for a constant value of $p=0.274$ and $q=0.726$.*

s	n_s	$1+\sum_{s=2}^{s} q^{s-1}$	$n_s \cdot s$	Expected no. affected	Observed no. affected
(1)	(2)	(3)	(4)	(5)	(6)
2	19	1.726000	38	22.016222	23
3	18	2.253076	54	23.967230	26
4	10	2.635733	40	15.176040	17
5	14	2.913542	70	24.025730	25
6	6	3.115231	36	11.556120	13
7	9	3.261657	63	19.315330	17
8	6	3.367962	48	14.251940	13
9	4	3.445139	36	10.449500	6
10	6	3.501170	60	17.137128	16
11	2	3.541849	22	6.211440	8
		Σ	467	164.106680	164

equation (2), $\sigma^{-2}=1{,}656.19$ and $\sigma=0.0246$. Thus, with HALDANE's method as well, there is satisfactory agreement with the expected value of 0.25 according to the hypothesis of monohybrid autosomal recessivity.

This value of p was calculated on the whole material. If the calculation is made on the 80 proband families only, a p value of 0.276 is obtained.

Table 9 shows a calculation of the expected number of affected in sibships of different sizes for $p=0.274$ and $q=0.726$. The different values of s from 2 to 11 are listed in column (1), the values of $(1+\sum_{s=2}^{c} q^{s-1})$ in column (3), and $n_s \cdot s$ in column (4). If the values in column (4) are divided by those in column (3), we obtain in column (5) the expected numbers of affected members in the whole observed group of families of size s, *i. e.*, n_s, given in column (2). In addition, column (6) shows r_s = the observed number of affected sibs in the respective groups of sibships of size s.

It can be inferred from Table 9 that fairly satisfactory agreement exists in the series between the expected and the observed number of affected members. It is, however, apparent that in the smaller families the observed values are slightly higher than the expected ones, whereas the reverse applies in the larger families. The two 11-child families are exceptions.

The observed number of affected members in all the families of the same size s is denoted as r_s, and $\sum_{s=2}^{c} r_s=R$ in equation (1). Using the same equation, q_s is then calculated, p_s being equal to $(1-q_s)$, but for each group of families of size s separately. Hence,

$$\frac{s \cdot n_s}{1+q_s+..+q_s^{s-1}}=r_s, \text{ and } \sigma^{-2}=\frac{r_s}{q_s(1-q_s)^2}-\frac{s^2 \cdot q_s^{s-2} \cdot n_s}{(1-q_s^s)^2}$$

The calculated values of p for different values of s, as well as the values of s, n_s and r_s, are given in Table 10. It is seen that the values of p — with the exception of $s=9$ — only deviate at random from the hypothesis 0.25, or from the actual mean value for the material, which is 0.274. It is nevertheless evident that with lower values of s, the values of p are higher, whereas with higher values of s, there is a trend to lower p values. Only for $s=9$ does a lower value, $p=0.105 \pm 0.065$, differ conspicuously from the average value of p for the whole material, according to the hypothesis of a monohybrid recessive mode of inheritance.

TABLE 10. *Calculation according to* HALDANE *of different values of p_s in groups of sibships of different size, s from 2 to 11, for (a) the whole material, (b) the proband families only.*

s =	1	2	3	4	5	6	7	8	9	10	11	Σ
						All families						
n_s	11	19	18	10	14	6	9	6	4	6	2	105
r_s	11	23	26	17	25	13	17	13	6	16	8	175
p_s	—	0.348	0.350	0.348	0.295	0.328	0.240	0.241	0.105	0.252	0.361	0.274
ε_P		±0.128	±0.089	±0.094	±0.066	±0.089	±0.062	±0.070	±0.065	±0.061	±0.105	±0.024
						Proband families only						
n_s	10	17	16	9	12	3	8	5	3	5	2	90
r_s	10	20	23	16	20	6	15	12	4	15	8	149
p_s	—	0.30	0.344	0.378	0.259	0.289	0.221	0.278	0.079	0.293	0.361	0.276

Let us therefore examine the group of four families in which $s=9$. They are families 10, 38, 41 and 90. F. 90 does not belong to any family complex; the parents are first cousins. Of 9 sibs, 2 are affected. The remaining 3 families belong to the large family complexes, which is a strong argument in favour of the same genetically conditioned disease being present in their case as well. In F. 41 (Su complex) there are 2 affected. The families mainly responsible for the low value of p are F. 10 and F. 38 (S and Su complex, respectively), each with only 1 affected out of 9 sibs. — In F. 90, the birth order of the affected members is 3 and 5, respectively. In F. 41, the birth order of the two affected members is 3 and 9, respectively. In F. 10 the birth order of the affected member is 9, and in F. 38, the birth order of the affected member is 6. One of the unaffected sibs in F. 10 has an affected son, who is now a pupil at Tomteboda Institute.

The same trend to a higher value of p with lower value of s, and *vice versa*, was present in SJÖGREN's investigation of juvenile amaurotic idiocy.

A reasonable explanation of the above observation is the psychological factor suggested by HALDANE (1932). This is that a number of parents may, after having produced one or two blind children, limit their families in future. Actually, it is surprising that large sibships with several members affected with such a severe congenital disease do, in fact, exist.

Probably, however, the conditions are complicated from a psychological point of view as well. A factor acting in the opposite direction probably operates in some parents.[1] After having produced one or more blind children, they may make further efforts, in the hope of having some healthy offspring as well. Interviews with the parents during the field work suggest that these two processes of thought acting in opposite directions — fears and hopes — may partly counterbalance each other in some way hard to understand, as is often the case with irrational, emotional forces.

It is nevertheless reasonable to assume that the resultant of such a play of forces acts to some degree in a family-limiting direction. Consequently, in a more enlightened community and when dealing with severe monohybrid genetic diseases with early manifestation, it is presumably necessary in family investigations to anticipate p values that

[1] *cf.* The investigations of RACE (1942) on the fertility of women with the semidominant trait acholuric jaundice, and those of GLASS (1950) on the fertility of Rh-negative white women.

TABLE 11. *Position in family of the affected.*

Number of children over 1 year of age in the sibship=s, number of such sibships=n_s, number of affected in the n_s sibships=r_s. In calculation of the birth order, only those children who reached one year of age are taken into account.

s	n_s	r_s	No. of affected with birth order no.											First half of sibship	Second half of sibship
			1	2	3	4	5	6	7	8	9	10	11		
1	11	11	11											.	.
2	19	23	13	10										13	10
3	18	26	11	5	10									13.5	12.5
4	10	17	7	4	3	3								11	6
5	14	25	5	4	5	6	5							11.5	13.5
6	6	13	1	4	3	2	1	2						8	5
7	9	17	2	1	3	2	3	2	4					7	10
8	6	13	1	—	1	2	1	4	1	3				4	9
9	4	6	—	—	2	—	1	1	—	—	2			2.5	3.5
10	6	16	2	2	2	1	—	4	—	4	—	1		7	9
11	2	8	2	2	1	1	—	—	—	—	1	1	—	6	2
Σ	105	175	55	32	30	17	11	13	5	7	3	2	—	83.5(89)	80.5(86)

somewhat exceed the expected value of $^1/_4$ if the trait is recessive, or $^1/_2$ if the trait is dominant.

The position of the affected children in the birth series (order of birth) is recorded in Table 11. Exogenous, non-genetic factors can be expected to result in an uneven distribution of the affected in this respect. A more even distribution can, on the contrary, be anticipated for genetically conditioned traits, provided that the age of the mother, for example, does not influence manifestation of the disease. Table 11 shows that 89 of the 175 affected cases occur in the first half of the birth series, and 86 in the second half.

As shown in Table 10, for $s \leq 6$, p was somewhat higher than the expected value of $^1/_4$, and for $s > 6$, p was slightly lower. It is seen from Table 11 that, for families with $s=1$ to 6, 62.5 cases occur in the first half of the birth series, and 52.5 cases in the second half. For families with $s=7$ to 11, the conditions are reversed; 26.5 cases occur in the first, and 33.5 in the second half.

In the birth series, we have 55 first-born and 51 last-born affected. The difference is again reversed for the two halves of the material with $s \leq 6$ and $s > 6$. In the smaller families, 48 first-born and 41 last-born are affected; the corresponding figures in the larger families are 7 and 10.

It is true that these figures are compatible with the aforegoing hypothesis of the family-limiting influence of the psychological factor, and its possible effect on the frequencies of affected individuals actually found in families of varying size. They can, however, as they are found in the birth series, also be due to chance.

Some further light can be thrown on this hypothetical factor by the following. Using the binomial theorem, the relative proportions of families with 1, 2 . . . to s affected in the group of families of size s are calculated. The distribution thus obtained for the group of families of each size of s are standardized as follows. The number of families with only 1 affected in the expected distribution is put equal to the corresponding number in the actually observed series of size s. This is done in Table 12. The expected and the observed series can then be compared.

We must examine the table with due reservation for the small size of the material, bearing in mind the influence of random variations. A consistent feature of the observed distribution is that, for lower values of s, some over-representation of families with > 1 affected exists, whereas in the distribution series for higher value of s, the reverse seems to apply.

It does not seem altogether unreasonable for the cause of this »skewness» to be the family-limiting factor of a psychological nature already discussed. In the absence of such a factor, some of the families with lower values of s and with > 1 affected child would be larger than they actually are. It seems possible that the skewness would then be evened out, or at least that the discrepancy beween the expected and the observed distributions would be of a less systematic appearance than is now the case.

However, the following objection can be raised. A psychological factor may, in fact, be active, but it is to be sought not in the parents of the affected, but in the investigator. Families with more than one affected member can more easily be detected, and it may be a question of purely inadvertent selection. Such a selection can be expected to be proportionately of greater consequence for smaller families. Such a factor of a large order of magnitude would be expressed in the relative distribution of the collected families among the varying sizes of s, as compared to that in the general population.

Data are available from the 1930 population census regarding the distribution of marriages by duration, age of the wife at marriage and number of children (Statistical Abstract of Sweden 1947, Table 25, p. 29). On the basis of these data, I have worked out a system of weights by

TABLE 12. *Expected (according to binomial theorem) and observed distribution of families of size s from 2 to 11, by number of affected from 1 to s in the families. In the standardization, the number of families with one child affected in the expected series has been put equal to the corresponding number in the actual observed series.*

s= / No. of affected	2		3		4		5		6		7		8		9		10		11	
	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.
1	15	15	10	10	4	4	4	4	1	1	3	3	3	3	2	2	2	2	0.3	—
2	2.5	4	3.3	8	2	6	2.7	9	0.8	3	3	4	3.5	—	2.7	2	3.2	—	0.6	—
3			0.4	—	0.4	1	0.9	1	0.3	2	1.6	2	2.5	2	2.1	—	2.7	2	0.6	1
4					.	—	0.2	—	0.1	—	0.5	—	1.1	1	1.8	—	1.6	2	0.4	—
5							.	—	.	—	0.1	—	0.4	—	0.3	—	0.6	—	0.1	1
6									.	—	.	—	.	—	0.1	—	0.2	—	.	—
7											.	—	.	—	.	—	.	—	.	—
8													.	—	.	—	.	—	.	—
9															.	—	.	—	.	—
10																	.	—	.	—
11																			.	—

means of which is obtained the expected distribution according to the number of children from 1 to ≥ 11 in the 100 marriages (legalized matings) in the present series (see Appendix 1, p. 121). This can then be compared with the actual observed distribution. In order to permit comparison with the data in the official statistics, the observed distribution has been made to comprise all the live-born children in the 100 sibships, including those who died before 1 year of age, but excluding those who died during labour or on the same day. The figures are shown in the following tabulation.

Family size, s	1	2	3	4	5	6	7	8	9	10	≥ 11
Exp. no. fam., n_s	10.3	15.9	16.2	14.0	11.4	9.2	7.3	5.6	4.1	2.8	3.3
Obs. no. of families	7	18	17	9	14	5	10	7	3	6	4

The observed distribution given in this tabulation differs slightly from that on which the Mendelian analysis was based. In the latter, those who had died before 1 year of age were excluded from the sibships.

Reservations must obviously be made for the disturbing effect of the many approximations, and for the purely random variations, in comparison of such a small sample obtained over such a long period with the data in the official statistics. Nevertheless, it seems worth noting the fairly good agreement between the two distributions. In any event, the figures do not lend support to the supposition that families with few children have been overlooked to any great extent in the course of assembling the material. Had this been the case, it would have occurred in assembling the cases at Tomteboda Institute, after their registration there. The account of the various diagnostic groups nevertheless shows that little opportunity existed of any cases being overlooked during this process.

Continuing the Mendelian analyses, the series may be classified from several viewpoints. The whole material can first be divided into the following groups of families:

a. The 23 families belonging to the 5 family complexes: *group FC.* (F. 9 and 10, which subsequently proved to be related to the S complex, have here been assigned to the next group in these calculations.)

b. The 14 families related by pair, consisting of 7 pairs unrelated to any other pair: *group FP.*

c. The remaining 57 families that could not be shown to be related in any way to other families with affected members: *group O.*

The genetic-statistical analysis of the three groups FC, FP and O with

TABLE 13. *Calculation according to* HALDANE *of expected number of affected in the material, divided into certain subgroups, for a constant value of p=0.274. For further details, see page 55—57.*

s	FC n_s	No. of affected exp.	obs.	FP n_s	No. of affected exp.	obs.	FC+FP n_s	No. of affected exp.	obs.	»Others» n_s	No. of affected exp.	obs.	ΣΣ n_s	No. of affected exp.	obs.	F 1928—38 at Tl n_s	No. of affected exp.	obs.
2	3	3.4762	3	2	2.3175	2	5	5.7937	5	14	16.2225	18	19	22.0162	23	8	9.2700	10
3	4	5.3261	6	2	2.6630	2	6	7.9891	8	12	15.9782	16	18	23.9672	26	7	9.3206	9
4	—	—	—	4	6.0704	6	4	6.0704	6	6	9.1056	11	10	15.1760	17	4	6.0704	6
5	4	6.8645	9	1	1.7161	2	5	8.5806	11	9	15.4451	14	14	24.0257	25	2	3.4322	3
6	2	3.8520	3	2	3.8520	5	4	7.7041	8	2	3.8520	5	6	11.5561	13	—	—	—
7	2	4.2923	3	1	2.1461	2	3	6.4384	5	6	12.8769	12	9	19.3153	17	—	—	—
8	1	2.3753	4	1	2.3753	3	2	4.7506	7	4	9.5013	6	6	14.2519	13	1	2.3753	1
9	2	5.2248	3	1	2.6124	1	3	7.8371	4	1	2.6124	2	4	10.4495	6	—	—	—
10	3	8.5686	8	—	—	—	3	8.5686	8	3	8.5686	8	6	17.1371	16	—	—	—
11	2	6.2114	8	—	—	—	2	6.2114	8	—	—	—	2	6.2114	8	—	—	—
	23	46.1912	47	14	23.7528	23	37	69.9440	70	57	94.1626	92	94	164.1064	164	22	30.4685	29

HALDANE's method is shown in Table 13. As earlier, the one-child families are excluded from the calculations.

It can be inferred from Table 13 that the expected and the observed number of affected members are in remarkably good agreement in all three groups. Differences which are probably random, are evident from the table. It is presumably justified to conclude that the three groups do not differ with respect to their agreement with the hypothesis of a monohybrid autosomal recessive mode of inheritance.

It was pointed out on page 12 that the registration of the blind in Sweden can be regarded as being more complete during recent years and that, since 1935, the only primary school for the blind is that at Tomteboda Institute. The Primary School for the Blind in Växjö was closed in the year in question. There are 22 families (plus 3 one-child families) which had some affected member, born between 1928 and 1938, at Tomteboda. It can be seen from Table 13 that the genetic-statistical analysis of these 22 families showed satisfactory agreement between the expected and observed number of affected. Evidently, the same is valid for the earlier part of the families.

The form of disease in question seems to be spread over the whole country, although there is every indication that its frequency varies in different regions. These matters will be discussed in later sections. Here, the genetic-statistical analysis is confined to the material grouped geographically as follows.

Table 14 on page 58 shows the distribution of the parents by the county in which they were born. As may be inferred from Table 25 and the map in Fig. 1 (p. 13), I have divided the whole country from north to south into five regions. The families have been grouped in these five regions according to the birthplace of the parents (see Tables 15 and 16). If both parents were born in the same region, the family is listed in the table under this region. If the parents (heterozygotes) were born in different regions, the family is listed under both regions. The observed number of affected members has then been compared with the expected number in the respective geographic regions (Table 16).

Of the 94 families with more than one child, 9 occur in two regions with respect to the parent's birthplace. The procedure in question is reasonable, since both parents must be given an equal value in this connexion. It is true that a slight spurious correlation between certain regions has been introduced by this procedure, but it can scarcely prevent a comparison and evaluation. As far as the more distant regions

TABLE 14. *The families distributed by county of birth of the parents.*

A single figure, *e. g.* 12 in column (3) for the county of Västerbotten, denotes that both parents in Family 12 were born in this county. The figure 16 ♂, for example, denotes that only the father in Family 16 was born in this county. The letters R, S, D—A, De and Su indicate complexes of related families. A number above the family number indicates the other family, for families related by pair. An italicized family number denotes that the parents are first-cousins. — The figures in column (2) give the number of parents (heterozygotes) born in the respective counties.

(1)	(2)	(3)										
		R	R	R	R	R	R		S	S	S	S
Norrbotten	22	1	2	3	4	5	6	7	8	9	10	11
		S		D	D	D	A					
Västerbotten	12	12	*13*	14	15	16♂	19♂	*27*♂	31♀			
		D	D	A								
Västernorrland	15	16♀	17	18	24♀	26	*27*♀	28	29	30		
		A	A	A	A	A						
Jämtland	12	19♀	20	21	*22*	23	24♂	25				
		De	Su	De	De							
Gävleborg	10	*32*	33	34	35	38						
Kopparberg	4	*36*	37									
		101										
Västmanland	1	52♂										
			85									
Upsala	2	43♂	50♂									
				85								
Stockholm county	5	45	46	50♀								
Stockholm city	2	49♀	51♀									
Örebro	2	44										
Södermanland	5	43♀	47	48								
			Su	Su	Su							
Värmland	9	31♂	39	*40*	41	42						
			55	54								
Göteborg and Bohus	13	53	54	55	*56*	57	58	73♂				
			65	64								
Skaraborg	10	63	64	65	66	*67*						
Älvsborg	10	49♂	59	*60*	*61*	62	68♂					
			70	69								
Halland	7	68♀	69	70	71♀	100♂						
Östergötland	7	72♂	77	*78*	79♀	82♂						
					81	80						
Jönköping	6	51♂	74♀	79♂	80	81♂						
						50						
Kalmar	12	72♀	82♀	83	84	85	*86*	88♀	89♀			
			80									
Kronoberg	7	71♂	81♀	89♂	*90*	*91*						
Blekinge	4	87	88♂	94♂								
Gotland	4	75	76									
Kristianstad	15	92	93	95	96	97♀	98	99	100♀	105♀		
		101					52					
Malmöhus	14	52♀	73♀	74♂	94♀	97♂	101	102	*103*	104	105♂	

TABLE 15. *Calculation, using* HALDANE's *method, of the expected number of affected in the material, divided into 5 large geographic regions according to the birthplace of the parents (see text, p. 57).*

I. Nb—Gb		No. of affected		II. Ko-Sö	No. of affected		III. Vä-Ha	No. of affected		IV. Ö-Kr-Bl	No. of affected		V. M-Kri	No. of affected	
s	n_s	exp.	obs.	n_s	exp.	obs.	n_s	exp.	obs.	n_s	exp.	obs.	n_s	exp.	obs.
2	4	4.6350	5	4 $_1$	4.6350	5	6 $_1$	6.9525	7	7 $_3$	8.1112	8	1 $_1$	1.1587	1
3	5	6.6576	8	1 $_1$	1.3315	1	5	6.6576	8	2	2.6630	3	6 $_1$	7.9891	7
4	—	—	—	1	1.5176	2	2	3.0352	3	4	6.0704	7	3	4.5528	5
5	6 $_1$	10.2967	11	2	3.4322	4	5 $_3$	8.5806	9	1	1.7161	1	3 $_2$	5.1484	6
6	2	3.8520	3	1	1.9260	3	3	5.7781	7	—	—	—	—	—	—
7	4	8.5846	7	—	—	—	2	4.2923	4	1	2.1461	2	2	4.2923	4
8	1	2.3753	4	1	2.3753	1	1	2.3753	1	3	7.1260	7	—	—	—
9	2 $_1$	5.2248	2	—	—	—	2 $_1$	5.2248	3	1	2.6124	2	—	—	—
10	4	11.4248	9	1	2.8562	3	—	—	—	1 $_1$	2.8562	4	1 $_1$	2.8562	4
11	2	6.2114	8	—	—	—	—	—	—	—	—	—	—	—	—
Σ	30 $_2$*	59.2622	57	11 $_2$*	18.0738	19	26 $_5$*	42.8964	42	20 $_4$*	33.3014	34	16 $_5$*	25.9975	27

* The small digits denote the number of families also represented in another geographic region, i. e. through the other parent.

TABLE 16. *A summary of calculations in Table 15.*

Geographic region	n_s		No. of affected exp.	obs.
I. Nb—Gb	30	2	59.3	57
II. Ko—Sö	11	2	18.1	19
III. Vä—Ha	26	5	42.9	42
IV. Ö—Kr—Bl	20	4	33.3	34
V. M—Kri	16	5	26.0	27
Σ	103	18*	179.6	179

* 9 families are counted twice, the parents being represented in two regions.

are concerned, for example the northernmost and southernmost, the comparison is fully correct.

It can be seen from Table 16 that, in all the geographic regions, the observed number of affected shows satisfactory agreement with the expected values according to the hypothesis set up.

Summary

As may be inferred from the genetic-statistical analysis in this section, the form of disease studied follows a monohybrid, autosomal and recessive mode of inheritance, with probably complete manifestation. Classification of the material from different viewpoints, such as the geographic origin, shows that it appears to be homogeneous with respect to this mode of inheritance.

The frequency calculated with HALDANE's method gives a somewhat higher value than the expected 25 per cent. The deviation may be random; $p=0.274\pm0.0246$. There is, however, reason to suspect that a psychological factor, with some family-limiting effect, may be active. The smaller sibships are thereby loaded with a slightly higher frequency of affected members than that expected according to the hypothesis. This seems to be a systematic phenomenon, and it has been discussed.

Naturally, the genetic-statistical analysis alone and in itself cannot elucidate whether we are dealing with a homogeneous pathologic condition, or with several such conditions genetically determined by different gene loci.

2. *Frequency of the Disease and Gene Frequency*

Let us set up the hypothesis that we are dealing with a homogeneous form of disease, determined by a gene at a specific locus. In the

TABLE 17. *Number of general population and of affected alive on Dec. 31, 1945, born between 1891 and 1938. Distribution by age groups. Statistical Yearbook 1950, Table 12, p. 14—15.*

Birth period	General population of Sweden			No. of affected		
	Males	Females	Both sexes	Males	Females	Both sexes
1891—00	410,489	429,653	840,142	12	8	20
1901—10	517,385	516,811	1,034,196	11	11	22
1911—20	546,819	532,312	1,079,131	13	21	34
1921—30	490,220	476,194	966,414	15	13	28
1931—38	341,182	328,020	669,202	11	13	24
Σ 1891—38	2,306,095	2,282,990	4,589,085	62	66	128

material consisting of the 105 families, 128 affected individuals (62 males and 66 females), born between 1891 and 1938, were alive on Dec. 31, 1945. The corresponding figure for the whole population of Sweden on the same date was 4,589,085 (2,306,095 males and 2,282,990 females). Table 17 gives the absolute figures, distributed by age group, and Table 18 the frequency figures calculated on the basis of these figures.

The difference between the sexes, as well as between the age groups, may — apart from the influence of random variations — be associated with the sources of error that are inevitable in all population statistics. The lower frequency in the older year groups may also be due to a mortality rate which is, in the long run, higher among the affected individuals than among the general population. A probable contributory factor is that, in recent years, the blind have been more effectively

TABLE 18. *Frequency of affected in the general population of Sweden, calculated from figures in Table 17. Estimation of frequency of the hypothetical gene r.*

Birth period	Males	Females	Both sexes
1891—00	0.00002923	0.00001862	0.00002381
1901—10	.00002126	.00002128	.00002127
1911—20	.00002377	.00003945	.00003151
1921—30	.00003060	.00002730	.00002897
1931—38	.00003224	.00003963	.00003586
Σ 1891—38	0.00002689	0.00002891	0.00002789
r	0.005186	0.005377	0.005281

TABLE 19. *Frequency of affected in the general population of Sweden. Persons born between 1891 and 1938 who survived one year of age. Estimation of frequency of the hypothetical gene r.*

(For calculations see Appendix 2, p. 122.)

Birth period	Males	Females	Both sexes
1891—00	0.00002942	0.00002369	0.00002661
1901—10	.00002035	.00003095	.00002554
1911—20	.00002501	.00004343	.00003403
1921—30	.00002954	.00002867	.00002911
1931—38	.00003152	.00003892	.00003514
Σ 1891—38	0.00002660	0.00003266	0.00002957
r	0.005158	0.005715	0.005438

registered, and also that stricter regulations have been enforced for their rational schooling.

The frequency of the disease in all those alive at the date in question, born during the 1891 to 1938 period, can thus be calculated from the table to be 2.8 in 100,000. Provided that there is a panmictic population in equilibrium, the gene frequency can be estimated at 5.3 in 1,000. On the basis of the discussion above, it would be reasonable to assume that the frequency figure for the youngest age group, *i. e.*, about 3.6 in 100,000, would be a better estimate of the actual frequency of the disease in the general population. The gene frequency could then be calculated to be about 6 in 1,000.

These figures are based on a cross census at a given time for all persons between certain age limits. We can make a longitudinal census in the following way, which also takes into account those who died before the end of 1945.

On the basis of the data from the official statistics, the number of all those born between 1891 and 1938 who reached one year of age can be calculated. (For the calculations, see Appendix 2, p. 122.) If all the affected inviduals in the material born during this period — who reached one year of age — are put in relation to these figures, the frequencies in Table 19 are obtained. The frequency figures in this table show a relatively good agreement with those in Table 18. One of the reasons for the difference between the frequency for the females in the two tables may be that the affected females seem to exhibit a higher mortality than that in the general population. — The average frequency of the disease, according to the calculations in Table 19, is about 3 in

TABLE 20. *Frequency of affected in the general population of Sweden. Children born between 1918 and 1937 who reached school age. Estimation of frequency of the hypothetical gene r.*

(For calculations see Appendix 3, p. 123.)

Birth period	Males	Females	Both sexes
1918—27	0.00002446	0.00002738	0.00002589
1928—37	0.00003260	0.00004111	0.00003678
Σ 1918—37	0.00002810	0.00003352	0.00003076
r	0.0053	0.0058	0.0055 ± 0.00035

100,000, and the gene frequency can be estimated at 5.4 in 1,000. In the case of the youngest age group we find, on the whole, the same somewhat higher estimation as that in Table 18.

We make a further attempt at a more direct calculation of the incidence of the disease in the general population. In »Microphthalmos and Anophthalmos with or without Coincident Oligophrenia», SJÖGREN and LARSSON (1949) made a calculation of the blind children who reached school age, *i. e.*, 7 years of age, born between 1918 and 1937. The corresponding figures for the general population are given in Table 6 on page 23 of their publication. On the basis of this table, I have calculated the frequency of the disease now being investigated for the same period as to age and time (Appendix 3, p. 123). In Table 20, the calculated frequencies are given, both for the whole period, and for the birth periods 1918—27 and 1928—37 separately.

It can be seen that the frequencies thus calculated agree on the whole with those given in Tables 18 and 19. It is reasonable to infer that the lower frequency for children born between 1918 and 1927 than for those born between 1928 and 1937 is partly to be ascribed to the factors already mentioned, *i. e.*, more complete registration, and enforcement of more rational education of blind children. Table 20 gives a frequency of the disease of about 3.1 in 100,000 for the children born between 1918 and 1937 who had reached school age. According to this calculation, the gene frequency can be estimated at 5.5 in 1,000.

We can now make an »indirect» attempt to estimate the average gene frequency in the population via a calculation of the parent matings, *i. e.*, the frequency of the hypothetical heterozygote×heterozygote matings, as follows.

The official statistics give the number of marriages contracted per year in the whole country (see Statistical Abstract of Sweden 1947,

TABLE 21. *Estimated number of marriages with at least one child contracted between 1891 and 1936 in the general population of Sweden. (Statistical Abstract of Sweden 1947, Table 38, p. 57 and Table 25, pp. 28—29). — Estimation of frequency in the general population of the hypothetical heterozygote × heterozygote matings.*

(For further details, see p. 66.)

Period	Marriages in general population			Marriages in parents of affected	Expected number of all heterozygote × heterozygote matings	Frequency of marriages of parents	Expected frequency of all heterozygote × heterozygote matings
	All	With at least one child					
	Total no.	Per cent of all	Absolute no.				
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
1891—00	292,760	(91)	266,412	15	23	0.00005630	0.00008633
1901—10	318,460	(91)	289,799	19	30.2	0.00006556	0.00010421
1911—20	357,610	90.9	325,067	19	32.8	0.00005845	0.00010009
1921—30	392,340	88.0	345,259	16	32.0	0.00004634	0.00009268
1931—36	284,930	82.6	235,352	13	27.0	0.00005524	0.00011472
Σ 1891—1936	1,646,100		1,461,889	82	145.0	0.00005609	0.00009919

Table 38, p. 57). The 1891—1936 period is that pertinent to the present material. The number of marriages contracted in the general population during different 10-year periods is shown in column (1) of Table 21. Since childless marriages are included, a correction must be made for them.

From Table 25 on pages 28—29 of the Statistical Abstract of Sweden 1947 it is possible to calculate the approximate frequency in per cent of childless marriages in the general population according to the duration of marriage, *i. e.*, from the time it was contracted until the 1930 census. The calculated frequencies agree on the whole with later calculations, *e. g.* the 1945 census, which might seem more appropriate for the present investigation. The 1930 census figures are, however, more detailed and informative than the 1945 figures. They have been taken as the standard for this reason; moreover, no great difference between them seems to exist.

In column (2) is shown the calculation on this basis of the expected number of marriages with at least one child as a percentage of those listed in column (1). Here, 1946 is taken as the end of the observation period. The absolute number of marriages to which the hypothetical heterozygote×heterozygote matings are then to be put in relation is given in column (3).

Between 1891 and 1936, 82 marriages (legalized matings) took place between the parents of the affected in the material. Their distribution among the different 10-year periods is shown in column (4). They should represent the known heterozygote×heterozygote matings in the whole country with at least one child and at least one affected child during the stated period. For the sake of simplicity, we can disregard the fact that one parent mating was homozygote×heterozygote.

The illegitimate alliances have not been included in the calculations. It is debatable whether one illegitimate parent mating, F. 51, should not rightly have been assigned to this category. This was not done. In this family with two children, the parents had lived together for many years in an alliance that did not differ in nature from a legitimate one. The other four illegitimate parent matings were, as far as could be judged, of a more transient nature.

If the figures in column (4) are divided by those in column (3), the frequencies in column (6) are obtained. It is immediately apparent that these figures are far too low to be a reasonable estimate of the frequencies of heterozygote×heterozygote matings in the general population. Whe have to complement them with the matings that can be ex-

pected to exist in the general population, with at least one child and *with no affected child* in the sibship. This has been done as follows.

The probability of producing one affected child is p and, consequently, that of producing an unaffected child is $q=(1-p)$. The number of »marked» heterozygote×heterozygote matings with at least one affected child and s children is n_s. The total number of heterozygote×heterozygote matings with at least one child, including those with no affected child, will then be

$$\frac{n_s}{1-q^s}.$$

The simplest way of making the calculations is for each marriage, *i. e.*, each hypothetical heterozygote×heterozygote mating, in the material with s children to be weighted with the factor

$$\frac{1}{1-q^s},$$

in which $q=(1-p)=0.75$ according to the hypothesis of monohybrid autosomal recessivity. According to the above definition, we get

$s=$	1	2	3	4	5	6	7	8	9	10	11
$\frac{1}{1-q^s}=$	4.0	2.3	1.7	1.5	1.3	1.2	1.2	1.1	1.1	1.1	1.0

Each »marked» heterozygote×heterozygote mating with $s=1$ could, on the average, be expected to represent 4 such matings, if those in the general population with no affected child were also taken into account. For $s=11$, the possibility is negligibly small of any heterozygote× heterozygote mating being without any affected child.

The figures thus weighted or standardized are recorded in column (5) of Table 21. It can be inferred from a comparison with column (4) that the 82 »marked», legalized heterozygote×heterozygote matings could be counted as corresponding to altogether 145 such matings, if those with no affected child are also taken into account. If the figures in column (5) are then put in relation to the figures in column (3), we obtain in column (7) the estimated frequency of heterozygote×heterozygote marriages in the whole population. For the whole period 1891—1936 this frequency is estimated at 0.00009919. Let r be the frequency in the population of the recessive gene in question. Assuming panmixia and genetic equilibrium, we may calculate the heterozygote frequency, gene frequency and homozygote frequency, as follows,

$$2r\ (1 - r) = 0.0098 (= \sqrt{0.000099})$$
$$r = 0.005$$
$$r^2 = 0.000025.$$

It can be pointed out that, in the course of the investigation, nothing emerged to support the assumption that the hypothetical heterozygotes differed, either physically or mentally, from the average conditions in the general population.

TABLE 22. *Survey of results of various ways of calculating the hypothetical gene frequency, homozygote and heterozygote frequency in the general population of Sweden, based on Tables 17—21, assuming panmixia and genetic equilibrium.*

	r^2	r	$2r\ (1-r)$
Both sexes			
No. born 1891—1938, alive Dec. 31, 1945	0.000028	0.0053	0.011
No. born 1891—1938, survived 1 yr. of age	0.000030	0.0055	0.011
No. of children reached school age, born 1918—37	0.000031	0.0056	0.011
No. of marriages 1891—1936	0.000025	0.0050	0.010
Males			
No. alive Dec. 31, 1945	0.000027	0.0052	0.010
No. born 1891—1938	0.000027	0.0052	0.010
No. of children of school age	0.000028	0.0053	0.011
Females			
No. alive Dec. 31, 1945	0.000029	0.0054	0.011
No. born 1891—1938	0.000033	0.0057	0.011
No. of children of school age	0.000034	0.0058	0.012

Summary

A survey of the frequencies estimated in various ways that have been discussed in this section is given in Table 22. In view of the deficiencies to which such calculations, based on the data in the official statistics, are liable, not to mention the deficiencies that may exist in the material investigated, conclusions can only be drawn with every reservation. It is nevertheless interesting — and even remarkable — to find the relatively good agreement between the calculations made in various ways. This applies not least to the agreement between the indirect calculations — via the marriages — and the more direct calculations. It would appear reasonable to assume the average frequency of the hypothetical disease to be about 3 in 100,000. Provided that panmixia and equilibrium are

TABLE 23. *Survey of ancestors traced through the parish registers and archives.*

Fam.	Generation														Total
	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	
1	2	4	8	16	26	36	34	58	63	15	1				263
2	2	4	8	14	26	28	26	39	24	6	1				178
3	2	3	5	8	12	20	33	55	31	8	1				178
4	2	4	8	16	28	46	51	25	21	20	16				237
5	2	4	7	8	12	23	31	45	26	1					159
6	2	4	8	15	21	34	50	49	71	65	14	1			334
7	2	4	7	14	26	38									91
8	2	4	8	14	20	19	4	5							76
9	2	4	8	14	22	26	3								79
10	2	4	8	14	20	25	10								83
11	2	4	8	12	16	9	4								55
12	2	4	8	12	24	26	10	10							96
13	2	4	8	16	12	4	2								48
14	2	3	6	12	20	19	11	2	1						76
15	2	4	8	12	12	7	2	1							48*
16	2	4	8	16	22	15	9	3	1						80
17	2	4	8	14	12	6									46
18	2	4	7	13	12	16	14	15	12						95
19	2	4	8	10	11	4	3	2	1						45
20	2	4	8	14	20	11	5	2							66
21	2	4	8	16	24	11	5	2							72
22	2	4	8	16	30	26	15	5	2						108
23	2	4	8	16	32	29	7	2	1						101
24	2	4	7	9	11	3									36
25	2	4	8	16	32	48	34								144
26	2	4	8	6											20
27	2	4	8	6	8	8									36
28	2	4	8	16	27	25	4								86
29	2	4	8	16	18	9									57
30	2	4	6	4	2										18

Fam.	Generation														Total
	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	
31	2	4	8	15	20	13	2								64
32	2	4	8	16	24	43	44	35	24	20	15	4			239
33	2	4	8	16	32	60	76	72	48	43	23	1			385*
34	2	4	8	13	20	38	72	94	96	67	61	29	1		505
35	2	4	8	14	27	40	17								112
36	2	4	8	2	2	2									20
37	2	4	8	16	25	16									71
38	2	4	8	16	30	53	46	40	15	14	6	1			235
39	2	4	8	16	32	64	102	89	27						344
40	2	4	8	16	30	55	47								162
41	2	4	8	16	28	10	2								70
42	2	4	8	16	30	46	43	15							164
43	2	4	8	10	16	17	14	1							72
44	2	4	8	16	27	42	49	18							166
45	2	4	8	16	26	22									78
46	2	4	8	16	32	50	64	18							194
47	2	4	8	16	20	26	20	8							104
48	2	4	7	9	14	8									44
49	2	4	8	8	14										36
50	2	2	4	2	2	4									16
51	2	4	8	6	10	3									33
52	2	2	4	8	16	14									46
53	2	4	8	16	20	18	4								72
54	2	4	8	16	20	22									72
55	2	4	8	12	14	12									52
56	2	4	8	12	19	2									47
57	2	3	6	1											12
58	2	4	8	10	4										28
59	2	4	8	15	18	8									55
60	2	4	8	16	18										48
61	2	4	8	16											30
62	2	4	8	12	16	6									48

Fam.	Generation														Total
	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	
63	2	4	8	16	16	16									62
64	2	4	8	16	12										42
65	2	4	8	14	16	4									48
66	2	4	7	10	8	4									35
67	2	4	8	16	32	32									94
68	2	4	8	2											16
69	2	4	8	16	30	24	12								96
70	2	4	8	16	16	9									55
71	2	4	8	4											18
72	2	4	8	12	2										28
73	2	3	5	5	6										21
74	2	4	7	6	8	6	2								35
75	2	4	8	13	24	6									57
76	2	4	8	16	32										62
77	2	4	8	6	6	4									30
78	2	4	8	8	8										30
79	2	4	8	8	6	3	3								34
80	2	4	8	14	18	13	7								66
81	2	4	8	10	10	8									42
82	2	4	8	16	22	30	16								98
83	2	4	8	16	25	15	2								72
84	2	4	8	16	15	15									60
85	2	4	8	14	20	1									49
86	2	4	8	14	10	5									43
87	2	4	8	2											16
88	2	4	8	8	4	2									28
89	2	4	8	16	25	28	2								85
90	2	4	8	14	24	28	29	22							131
91	2	4	7	14	8	4									39
92	2	4	8	8	14	18	19	4							77
93	2	4	8	9											23
94	2	3	6	10	12										33

Fam.	Generation														Total
	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	
95	2	4	8	6	2										22
96	2	4	8	2											16
97	2	4	8	5											19
98	2	4	6												12
99	2	4	7	8											21
100	2	4	8	2											16
101	2	4	8	14	14	6									48
102	2	4	4	8											18
103	2	4	8	13											27
104	2	4	8	4											18
105	2	4	6	4											16
1—105	210	411	801	1,221	1,609	1,546	1,061	736	464	259	138	36	1		8,060*

* In the figure 8.060 the ancestors of fam. 15 and 33 are not included, since they occur in fam. 16 and 34 respectively, one generation earlier (with one number higher).

present, the gene frequency can be estimated at 5 to 6 in 1,000, and the heterozygote frequency at about 1 in 100.

3. *Frequency of Consanguineous Marriages*

Of the 105 families in the material, the parents were first cousins in 17 cases, in 6 others they were second cousins, and in an additional 22 families a more distant relationship existed between the parents. This gives for the investigated families a mean coefficient of inbreeding (α) of at least 0.01, *i. e.*, about 5 to 10 times higher than can be expected in the general population of Sweden. As far as first and second-cousin relationships are concerned, the investigation of the material should be practically complete. With respect to more distant relationship of the parents, the investigation is naturally incomplete and largely heterogeneous. This can be inferred from Table 23 (p. 68) showing the number of investigated ancestors per family.

Of the 105 matings, 5 are illegitimate. These are F. 6, 16, 18, 50 and 51. The two first-mentioned families each belong to a large family complex, R and D, respectively. In both cases, the parents are related 5—5.

F. 50 is related to the »legitimate» family F. 85. Reference is made to page 65 for a discussion of the »legitimacy» or »illegitimacy» of F. 51.

A first-cousin relationship thus exists in 16.2±3.6 per cent of the hypothetical heterozygote×heterozygote matings. Of the 35 families in the north of Sweden, there is a first-cousin relationship in 17.1 per cent, the corresponding figure for the 70 families in the rest of the country being 15.7 per cent.

A comprehensive and instructive discussion of the problem of consanguineous matings in different human populations, and the possibility of estimating the gene frequency of rare recessive traits by means of them, is found in a paper by NEEL *et al.* (1949). They also give a survey of investigations regarding the frequency of first-cousin marriages in different European countries.

Even if a frequency of a 2—2 relationship (first-cousin marriage) amounting to 0.01 may be too high for most contemporary European countries, we must agree with NEEL *et al.* that it probably approximates the true value for not too long ago. Moreover, in the Scandinavian countries, with their more settled population, we can expect a higher incidence of consanguineous marriages than on the continent. The incidence of such marriages can also be expected to vary even in different parts of the same country, for example to be lower in large towns and higher in rural districts.

SJÖGREN (1948) and LARSSON and SJÖGREN (1954) found, in a west Swedish rural population, a 2—2 relationship among parents of children born between 1861 and 1920 amounting to 2.6±0.6 per cent and 2.3±0.5 per cent for the »native» and the resident population, respectively. BÖÖK (1948) found a 2—2 frequency of 2.2±0.4 per cent among the existing marriages in 1947 in the three parishes in the northernmost part of Sweden. The differences between the parishes were, however, considerable. The respective frequencies were 1.0, 2.9 and 6.8 per cent.

Several authors have worked out formulae giving the relation between r=the frequency of a recessive gene responsible for the trait in question, k=the frequency of first-cousin marriages among the parents of the affected, and c=the frequency of first-cousin marriages in the general population from which the sample of the affected is drawn. The following has been given by WEINBERG (1920) and by DAHLBERG (1929).

$$r=\frac{c(1-k)}{16k-15c-ck}$$

A condition for application of the formula is panmixia and equili-

TABLE 24. *Different values of r according to* WEINBERG's *formula,* $r = \frac{c(1-k)}{16k - c(15+k)}$, *in which c is the frequency of first-cousin marriages in the general population, k is the same frequency in the parents of the affected, and r is the gene frequency of the trait in question.*

c	Values of r for $k = 0.162 \pm 0.036$			Values of r^2 for $k = 0.162 \pm 0.036$		
	$(k-\varepsilon_k)$	$(k \pm 0)$	$(k+\varepsilon_k)$	$(k-\varepsilon_k)$	$(k \pm 0)$	$(k+\varepsilon_k)$
0.010	0.0047	0.0034	0.0027	0.000022	0.000012	0.000007
0.011	0.0052	0.0038	0.0029	0.000027	0.000014	0.000008
0.012	0.0057	0.0042	0.0032	0.000032	0.000018	0.000010
0.013	0.0062	0.0045	0.0035	0.000038	0.000021	0.000012
0.014	0.0068	0.0049	0.0038	0.000046	0.000024	0.000014
0.015	0.0073	0.0053	0.0041	0.000053	0.000028	0.000017
0.016	0.0079	0.0057	0.0044	0.000062	0.000033	0.000019
0.017	0.0084	0.0061	0.0047	0.000071	0.000037	0.000022
0.018	0.0090	0.0065	0.0050	0.000081	0.000042	0.000025
0.019	0.0096	0.0069	0.0053	0.000092	0.000048	0.000028
0.020	0.0102	0.0073	0.0056	0.000104	0.000053	0.000031

brium in the population in question. Complete panmixia can scarcely be envisaged as existing in human populations, as little as can complete isolation barriers between the different partial populations. The various difficulties encountered in use of the formula have been thoroughly discussed by NEEL *et al.* (1949). With all necessary reservations, tentative calculations may be permissible.

Using the above formula, calculations are shown in Table 24 of r and r^2 for values of c ranging from 0.01 to 0.02, as well as for the three values $(k - \varepsilon_k)$, $(k \pm 0)$ and $(k+\varepsilon_k)$, in which $k \pm \varepsilon_k$ is 0.162 ± 0.036.

In the preceding section, the frequency of recessives could be estimated by other means at 0.00003. This value is recorded in the right half of Table 24, for $k=0.162$ and values of c at about 0.015 or 0.016. This seems to be a plausible estimate of the over-all frequency of first-cousin marriages in the whole population of Sweden during the period in question.

If we confine the calculations to the marriages contracted by the parents between 1891 and 1936, about 20.7 per cent of those in the material were first cousins. According to Table 22 on page 67, the frequency of recessives in the general population could be estimated, by means of the »heterozygote×heterozygote matings», to be 0.000025.

This value in column $(k+\varepsilon_k)$ in Table 24 then gives an estimation of c in the general population amounting to 0.018.

Let us, however, assume the best estimate of the frequency of recessives to be 0.00003, a reasonable over-all value of the frequency of first-cousin marriages in the general population to be 0.015 during the period in question, and the frequency of second-cousin marriages to be half of this value. We can then calculate WRIGHT's mean coefficient of inbreeding (F) for the general population or, according to HALDANE, instead of F, use the symbol α (BERNSTEIN). It will be at least 0.0011 and

$$r^2+\alpha r(1-r)=0.00003$$
$$\therefore r=0.005$$

and the frequency of heterozygotes in the general population could be estimated at $2r(1-r)(1-\alpha)\sim 0.01$. An estimation of r by directly taking the square root of 0.00003 would have given a somewhat higher value, *i. e.*, 0.0055.

In view of the large sources of error and of the difficulties both of a theoretical nature in connexion with the calculations, and of those associated with the material itself, many of the foregoing calculations may appear to be superfluous. They seem, however, to show a reasonable agreement between different approaches in attempts to determine the hypothetical gene frequency and heterozygote frequency. The tentative nature of the calculations must nevertheless be borne in mind.

SJÖGREN (1931), in his work on juvenile amaurotic idiocy, calculated the frequency of recessives in this disease in the general population to be about 0.000038, the frequency of heterozygotes to be 0.012, and the gene frequency to be 0.0062, according to the HARDY—WEINBERG law. At that time, little or nothing was known of the actual frequency of first-cousin marriages in the general population of Sweden. This matter was not investigated until a later date by SJÖGREN himself (1948, 1954) and by BÖÖK (1948).

Using WEINBERG's formula given above, SJÖGREN assumed a value of 0.01 for c. For $k=0.15$ found in his material, he obtained $r=0.0038$. However, as he himself subsequently showed, the value of c should lie between 0.02 and 0.01, in any case for the period in question in his material. The formula then gives a value for r and for the frequency of heterozygotes very close to his directly calculated value. SJÖGREN was very cautious in drawing conclusions, and stressed the importance of the fact that the gene frequency appeared to be higher in certain regions of Sweden than in others.

In a criticism of calculations performed, as the aforegoing, with WEINBERG's formula in rare recessive diseases, DAHLBERG stated(*e. g.* 1938, 1943) that the real heterozygote frequency for juvenile amaurotic idiocy in Sweden »as related to the entire population amounts to only a small fraction of 1 per cent». NEEL *et al.* (1949) referred to this criticism, and added: »It is unfortunate that in this rather knotty situation DAHLBERG did not publish figures to support his argument». And what is needed here is investigations of actually existing conditions. An attempt by DUNN (1947) to attack the problem more concretely showed good agreement with SJÖGREN's calculations.

It is of interest to note that the frequency figures in SJÖGREN's material and those in the present investigation — both obtained from the same source, the organizations for the blind in Sweden — happen to be of the same order of magnitude.

Summary

The frequency of consanguineous marriages in the material has been calculated. The corresponding frequency in the general population is discussed. The frequency of cousin marriages determined for certain populations in various parts of Sweden (SJÖGREN, LARSSON and SJÖGREN, BÖÖK) is also discussed. Using WEINBERG's formula and making the highly hypothetical assumption of panmixia and genetic equilibrium in the general population of Sweden, a tentative calculation has been made of the gene frequency and heterozygote frequency in the disease under investigation. It is pointed out that, with due reservations, these calculations show satisfactory agreement with the more direct frequency calculations made in the preceding section.

4. *Geographic Distribution*

The country of Sweden is divided into 25 large administrative regions, the capital (Stockholm), and 24 counties. In Table 25, they are listed from north to south and numbered; these numbers are also given on the map (Fig. 1, p. 77). For the general population, data are given in the Statistical Abstract of Sweden 1950 (Table 13, pp. 16—17) regarding the age distribution by county of those alive on Dec. 31, 1945, aged from 10 to 49 years. The next age group, 50 to ω years, is an »open» class in the aforementioned table. The number of affected persons alive on this date, and between the age of 10 and 49 years, amounted to 108. They

TABLE 25. *The frequency of a) the affected (recessives) per 10.000, b) the gene frequency per 100, c) the heterozygote frequency in fractions of unity in the general population by county. Estimations made on the basis 1) of the age groups 10—49 alive on 31/12 1949, 2) of the marriages contracted in the years 1891—1936. For basic numbers see Table 26 and Appendix 4.*

County	Homozygote frequency per 10,000		Gene frequency per 100		Heterozygote frequency (fractions of 1)	
	Age 10—49 (1)	Marriages 1891—36 (2)	Age 10—49 (3)	Marriages 1891—36 (4)	Age 10—49 (5)	Marriages 1891—36 (6)
I						
1 Norrbotten	0.93	0.43	0.96	0.65	0.019	0.013
2 Västerbotten	0.36	0.42	0.60	0.65	0.012	0.013
3 Västernorrland	0.36 0.51	0.33 0.39	0.60 0.71	0.57 0.62	0.012 0.014	0.011 0.012
4 Jämtland	0.72	0.40	0.85	0.63	0.017	0.013
5 Gävleborg	0.31	0.40	0.56	0.63	0.011	0.013
II						
6 Kopparberg	0.14	0.15	0.37	0.39	0.007	0.008
7 Västmanland	0.09	0.05	0.30	0.22	0.006	0.004
8 Uppsala	0.12	0.13	0.34	0.37	0.007	0.007
9 Stockholm county	0.21 0.13	0.08 0.08	0.46 0.35	0.29 0.29	0.009 0.007	0.006 0.006
10 Stockholm city	0.02	0.04	0.16	0.20	0.003	0.004
11 Örebro	0.29	0.10	0.54	0.32	0.011	0.006
12 Södermanland	0.17	0.09	0.41	0.31	0.008	0.006
III						
13 Värmland	0.19	0.27	0.43	0.52	0.009	0.010
14 Göteborg and Bohus	0.26	0.18	0.52	0.42	0.010	0.008
15 Skaraborg	0.36 0.25	0.29 0.25	0.60 0.50	0.54 0.50	0.012 0.010	0.011 0.010
16 Älvsborg	0.20	0.34	0.45	0.58	0.009	0.012
17 Halland	0.22	0.24	0.47	0.49	0.009	0.010
IV						
18 Östergötland	0.21	0.32	0.45	0.57	0.009	0.011
19 Jönköping	0.20	0.17	0.45	0.41	0.009	0.008
20 Kalmar	0.45 0.32	0.55 0.33	0.67 0.57	0.74 0.58	0.013 0.011	0.015 0.012
21 Kronoberg	0.23	0.35	0.48	0.59	0.010	0.012
22 Blekinge	0.35	0.18	0.59	0.41	0.012	0.008
23 Gotland	1.20	0.56	1.09	0.75	0.022	0.015
V						
24 Kristianstad	0.62	0.53	0.79	0.73	0.016	0.015
25 Malmöhus	0.15 0.30	0.24 0.33	0.39 0.55	0.49 0.57	0.008 0.011	0.010 0.011
Total	0.27	0.25	0.52	0.50	0.010	0.010

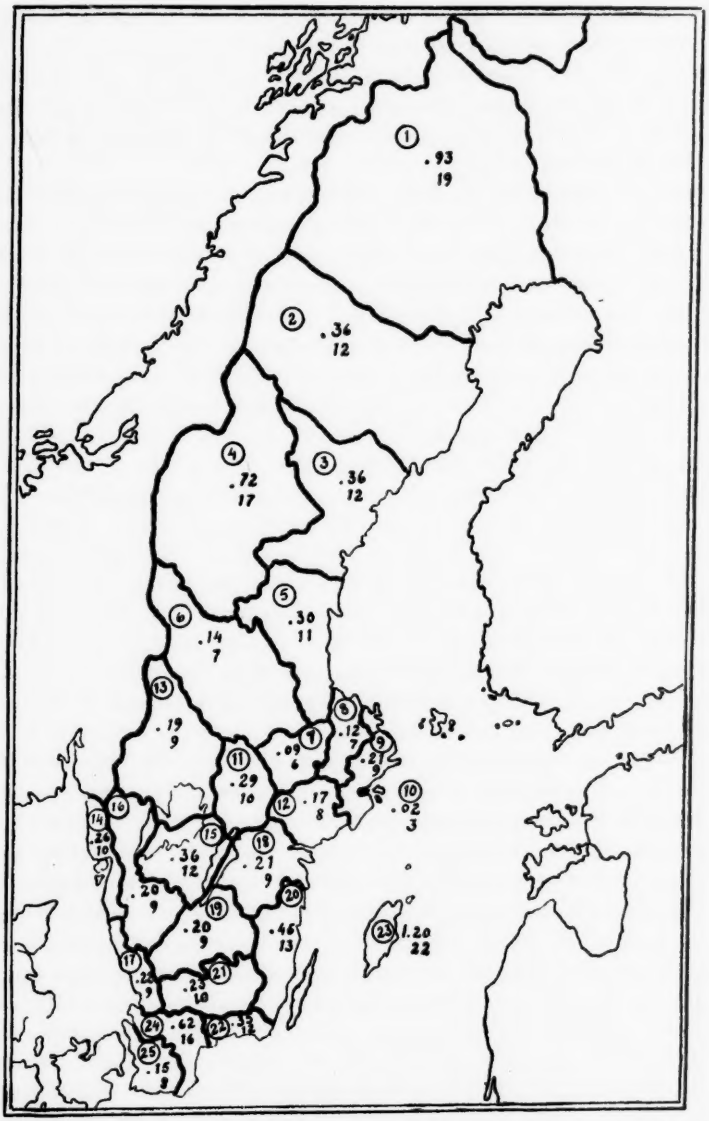

Fig. 1. Map showing homozygote and heterozygote frequency by county. Encircled numbers indicate counties; decimal numbers, e. g. .93, denote homozygote frequency per 10.000, and whole numbers, e. g. 19, denote heterozygote frequency per 1.000.

have been distributed by county according to their birthplace. This distribution of the affected persons is the most rational one. Their distribution by place of residence at the date in question would have led to entirely irrational values. The social organizations for blind adults have resulted in their becoming concentrated in certain regions, particularly in the capital, Stockholm.

As shown in Table 25 I have divided the country into five large regions, on possibly more or less debatable geographic and demographic grounds. These regions, also arranged from north to south, are denoted as I, II, III, IV and V. The figures on which the calculations in Table 25 are based are found in Table 26 and Appendix 4 (p. 124). It must be emphasized that the number of recessives in some counties is very small, being only one or two persons (*cf.* Table 26, p. 87). Consequently, every reservation must be made in drawing conclusions as to the conditions in individual counties.

Column (1) in Table 25 (p. 76) shows calculations of the average frequency of recessives in each county, in each of the five large regions, and in the whole country. It can be seen that there are fairly large differences between the counties. On the whole, the frequencies are higher in the northernmost counties. The highest frequency, however, is found on the island of Gotland in the Baltic which, to a greater extent than other parts of the country today, can be regarded as a genetic isolate. It is, however, interesting to note that a high incidence of the disease seems to be present in the county of Kristianstad, the most southernmost county but one in Sweden.

The lowest frequency of the disease is in the capital, Stockholm, which is not surprising, as we are dealing with a rare recessive defect. Stockholm is the largest, most fluctuating population area in the country, with considerable migration in and out, and a population which has grown from about 300,000 in 1900 to about 710,000 in 1948.

The gene frequency and heterozygote frequency by county, calculated according to the HARDY—WEINBERG law, are recorded in columns (3) and (5) of Table 25. The heterozygote frequency has been put equal to approximately twice the gene frequency. The average heterozygote frequency in the northernmost large region, given immediately to the right of column (5), is 0.014, the range in the different counties being 0.011 to 0.019. For the large population region in the middle of Sweden, the mean heterozygote frequency is half this figure, or 0.007, with a range for the different counties of 0.006 to 0.011. The corresponding figure for Stockholm is 0.003.

The conditions are, on the whole, similar for the large geographic regions in the south of Sweden, with a range for the different counties of 0.08 to 0.013, around average values of 0.010 and 0.011 calculated for the whole regions. Deviations from this range are found in the county of Kristianstad with a calculated heterozygote frequency of 0.016, and Gotland. The latter region, which should actually be treated separately on account of its geographic position, has the highest heterozygote frequency calculated for any county, *i. e.*, 0.022.

If the effect of inbreeding, calculated according to WRIGHT's mean coefficient of inbreeding, is taken into account, we obtain a slight decrease in the highest heterozygote frequencies, but scarcely in the others. In view of the deficiencies that may be present both in the material and in the data in the official statistics, no correction has been made for the frequency of inbreeding.

The figures in columns (1) and (5) of Table 25 are given on the map (Fig. 1). With the reservations made earlier, the frequencies stated should give some conception of the geographic variation of the disease. It is also of interest to note that it seems to occur scattered over the whole country.

The following »indirect» attempt to estimate the frequency of the disease, the gene frequency and heterozygote frequency by county has been done in a similar way to that described for the whole country (*cf.* p. 66 and Table 21). The calculations have been made on the basis of the marriages contracted between 1891 and 1936, with at least one child and at least one affected child. Correction for the hypothetical heterozygote×heterozygote matings with at least one child but no affected child has been made by weighting the individual marriages in the way stated. The marriages in the general population of Sweden contracted between 1891 and 1936, with the aid of hypothetical approximations and classified by county, are given in Appendix 4 (p. 124). The frequencies obtained are recorded in columns (2), (4) and (6) of Table 25 on page 76.

In view of the approximations that must be made in order to use the data in the official statistics for this purpose, it is remarkable to find the relatively good agreement between this »indirect» calculation and the direct one discussed above. As far as the mean values for the five large geographic regions are concerned, the agreement is even very good. The variation within the different large regions is also, on the whole, similar to that obtained by direct calculation.

In the following tabulation, the frequency of first-cousin relationships

is given for all the parents, *i. e.*, all the 105 parent matings in the material, distributed over the five large geographic regions. In addition, the mean gene frequency in these regions, estimated by the direct method, is given (*cf.* the figures directly to the right of column (3) in Table 25, p. 76). On the basis of these observed values, calculations have been made of the frequency of first-cousin marriages (*c*) for the general population in these regions, using WEINBERG's formula given on page 72.

Region	*Obs. k*	»*Obs.*» *r*	$c = \frac{16 \cdot rk}{1 - k + r(15 + k)}$
I. Nb—Gb	0.17	0.0071	0.021
II. Ko—Sö	0.10	0.0035	0.006
III. Vä—Ha	0.20	0.0050	0.018
IV. Ög—Gl	0.20	0.0057	0.021
V. Ma—Kr	0.07	0.0055	0.006
Whole country	0.16	0.0052	0.014

The values of *c* calculated in this way seem to be fairly reasonable estimates of the mean frequency of first-cousin marriages in the general population in these regions during the period in question. Obviously, as pointed out earlier, conclusions can be drawn only with the utmost caution. For instance, it is immediately evident that the frequency of consanguineous marriages in *e. g.* the greater part of the county of Kopparberg was probably considerably higher than the mean value, 0.006, estimated for the larger region in which the county is included in these calculations.

Summary

The administrative districts into which Sweden is divided are listed. For the purpose of the investigation, the country is divided into five large population regions. An analysis has been made of the gene frequency, heterozygote frequency and homozygote frequency in these regions with respect to the disease studied. This has been done under the hypothetical assumption that it is a genetically homogeneous form of disease.

The disease seems to be spread over the whole country, but with a varying frequency. The highest frequency (apart from the island of Gotland in the Baltic) is found in the northernmost region, and the next highest in the southernmost region. The lowest frequency is noted in the middle and presumably most fluctuating population region and in the capital, Stockholm.

The incidence of consanguineous marriages in the various geographic regions is discussed.

5. *Discussion of the Genealogical Investigations*

In the course of the genealogical investigation, more than 8,000 ancestors were traced (Table 23). In the northern part of Sweden, in which the population is both sparser and more settled, more intensive research could be done. In the southern part, with its denser and more fluctuating population, the conditions were less favourable. Here, any connexions that might have existed between various families were presumably too long ago to be established with any certainty.

It was found that, in the present material, a number of families in the north of Sweden belonged to large family complexes. These can be studied in Tables 2, 3 and 14 and Figs. 2 and 5 to 9. The geographic range of all the ancestors traced in the respective family complexes is shown in Fig. 2. It is seen that they are spread over fairly large regions. It is interesting to note how they succeed each other from the north southernwards, with inappreciable overlapping.

The northernmost, denoted as the *R* complex, situated in the county of Norrbotten, comprises 6 families (Fig. 5). Naturally, it has been impossible to insert all traced ancestors in the pedigree, but only certain of them in which convergence has been demonstrated are shown. The earliest ancestral pairs (denoted as I—VII) derive from the coastal region in the geographic range of the family complex. It seems reasonable to assume that the gene has spread along the valleys in the county of Norrbotten from this coastal region, which was formerly a central one from the population viewpoint. It is evident from Fig. 5 that no less than 5 of the families in the complex can be traced to a common pair of ancestors in the 17th century. These descendants are denoted by broken lines in Fig. 5. Above families 3 and 6, it can be observed how, in the lines descending from this ancestral pair (denoted as VI), the disease seems to have appeared in the 1820's and the 1790's, respectively. The individuals denoted by ◒ are stated to have been blind since birth or early childhood. Nothing more is known about them. The great majority of the ancestors in the *R* complex belong to the county of Norrbotten, and only a minor part to the county of Västerbotten, but a few ancestors are found as far south as the county of Gävleborg, in a region adjacent to the *De* complex.

The geographic range for the ancestors of the *S* complex, comprising

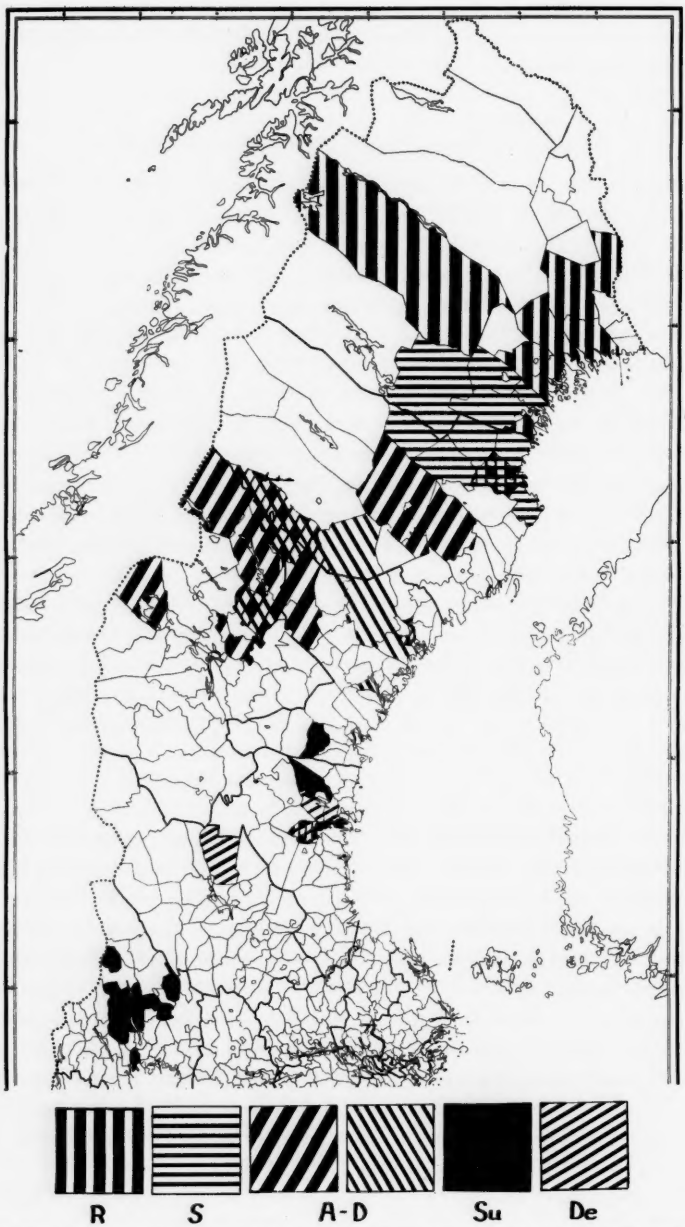

Fig. 2. Map showing the birth parishes of all traced ancestors in the large pedigree complexes.

5 families (and one additional family traced later: see Appendix 6, p. 132, under F. 10, and Fig. 6) is the south-eastern part of the county of Norrbotten and the north-eastern part of the county of Västerbotten.

The marriage of proband F. 11 b is interesting (see Fig. 6). He married an unrelated schoolmate from Tomteboda, suffering from cataracta congenita. The woman was from a parish in the northernmost part of the county of Norrbotten, and was of Finnish origin, whereas the proband 11 b, as far as could be ascertained, had no Finnish ancestors. (There are, however, a few ancestors of Finnish origin in the *R* and *A—D* complexes.) They had two boys, one of whom has cataracta congenita, like the mother. In her family, cataracta congenita has now occurred in in four successive generations. The other boy has normal sight. It is evident that, in this family, there is a coincidence of two genetically different disease, the recessive one comprising the disease studied in the present investigation, and the dominant one of cataracta congenita. It is, so to speak, a proof of Nature itself that these two hereditary phenomena are genetically separate entities.

South and west of the aforegoing family complex, follows the *A—D* complex (see Fig. 2). In the genealogical study, two separate complexes were first traced, which essentially overlapped with respect to the geographic range of the ancestors (Table 14 and Fig. 7). They comprise altogether 10 families (or 9, since two sibships are half-sibs). The earliest ancestral pairs (denoted as I—X) all have their geographic origin in the valley of S—m and the forest regions east of it, the former having long been a central population region. The geographic range of the ancestors of the *A—D* complex lies in the counties of Västerbotten, Jämtland and Västernorrland. It is not unreasonable to assume that the gene could have been spread chiefly over these counties from the population region in the valley of S—m.

The *De* complex occurs further south, in the county of Gävleborg (Figs. 2 and 8). A small proportion of the ancestors of the families belonging to this complex are also found in the county of Dalarna. The absolute majority of them have, however, for centuries been born, lived and died in a geographically relatively limited region. In this respect, the *De* complex might be said, to a greater degree than any other family complex investigated, to have the stamp of an »isolate». We are not, however, dealing with a remote, cut-off »isolate settlement». On the contrary, the *De* complex is interposed in a long well-populated agricultural settlement, lying centrally in the county on the shores of the

D lakes, and having good communications with the nearby coastal region.

It is interesting to note that in F. 38 (Su), belonging to the last large family complex — the *Su* complex further southwards — half of the ancestors, on both the paternal and the maternal side, derive from this population region with the *De* complex around the D lakes (see ancestral pair XII in Fig. 9). Both parents of F. 38 (Su) were born in this region (see Table 14). Some of the ancestors of F. 38 (Su) come from a part of the county of Västernorrland adjacent to this region (Fig. 2).

The *Su* complex is the southernmost of those investigated. It consists of 4 families, and one additional family with two reputed affected, blind since birth according to the parish registers and to information obtained in the field studies (see Fig. 9). The geographic range of the ancestors of these families is, in this county as well, to be found mainly in a centrally situated population region, the F—s valley. With respect to F. 38 (*Su*), see above. On the paternal side, F. 31 derives from this population region, and on the maternal side from the county of Västerbotten, a coastal region wedged in between the *A—D* and *S* complexes (Table 14). No genealogical connexions could be demonstrated between F. 31 and the *Su* complex.

Apart from the *Su* complex, no family complexes were traced in central and southern Sweden. On the other hand, the field investigations and genealogical studies disclosed, scattered over the country, six pairs of families related by pair. They are families 50—85, 52—101, 54—55, 64—65, 69—70 and 80—81. It is evident from Table 14 that the first two pairs have ancestors represented in widely separated parts of the country. It can also be inferred from Table 14 that the parents in an additional five single families — 43, 49, 51, 73 and 74 — come from regions at a great distance from each other, and a further number from counties adjacent to each other. In the regions of the family complexes in the north of Sweden already discussed, there also occur, as seen in Table 14, a number of families in which no connexions with these family complexes could be demonstrated.

In Fig. 3, the parishes of birth of the 210 parents in the total 105 families in the present investigation are recorded on a map of Sweden. The wide scattering over the whole country is evident, every county being represented.

Finally, it may once again be emphasized that the partial concentration of remote ancestors that could be demonstrated in the five large family complexes *R*, *S*, *A—D*, *De* and *Su* was not localized to those

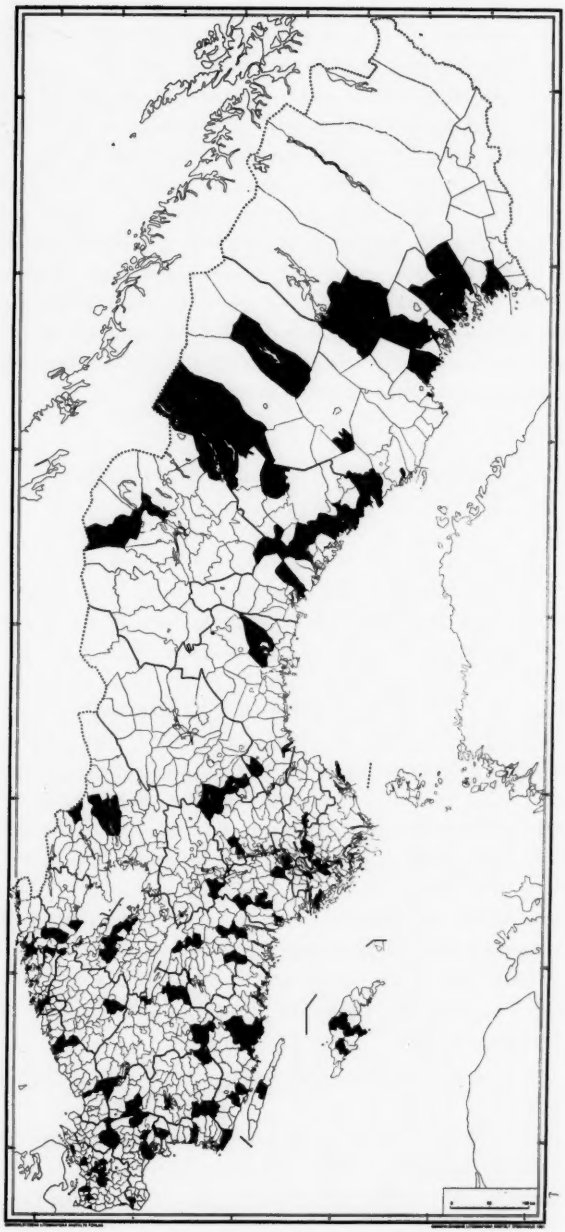

Fig. 3. Map showing the birth parishes of the parents in all 105 families.

parts of the counties most markedly of an »isolate» nature. On the contrary, it occurred in the more central regions from the point of view of population, with good geographic communications, and seemingly good channels to other partial populations or to the population as a whole. Judging by the genealogical studies, the population movement to more remote regions seems to have been sluggish in comparison with that in the regions in question. This may appear self-evident. It nevertheless seems to depend to a greater extent on the question of distance than on topographical obstacles. This is only a surmise. From the point of view of population genetics, an empiric study of the population movements in the past would be of great interest. Obviously, only such a study can give definite information about the dynamics and structure of these conditions.

6. *Frequency of Heterozygotes Calculated under Different Conditions. Effect of Isolates*

The parishes of birth of the parents are shown in Fig. 3 (p. 85). Column (1) in Table 26 shows, by county of birth from north to south, the number of affected individuals alive on Dec. 31, 1945, aged 10 to 49 years; altogether 108 persons. In column (2) is given, for each county, the size of the population aged 10 to 49 years, and in column (3) the population in the birth parishes of the affected persons alive on Dec. 31, 1945. These latter figures thus denote the population only in those areas in which the affected persons were born, and not in the whole county. The figures were obtained from the data in the official statistics, the sources being Kommunindelningen (Division into Communes) 1945, 1950, Statistical Abstract of Sweden (1950) and THUNBORG (1950).

Estimations of the hypothetical heterozygote frequency in the respective counties under various premises are given in columns (4) to (6). In addition, figures are given, as proportions of the population in each whole county on Dec. 31, 1949, for the population in the parishes of birth (birth region), for:

a) The 108 affected persons alive on Dec. 31, 1945, aged 10—49 years: column (7);
b) The total 175 affected persons in the material: column (8);
c) The total 210 parents in the material: column (9);
d) The birth region of the 108 affected persons alive on Dec. 31, 1945,

TABLE 26. *Frequency of heterozygotes by county, calculated under various assumptions.* (For further explanation, see below and p. 86.)

TABLE 26. ***Frequency of heterozygotes by county, calculated under various assumptions.***
(For further explanation, see below and p. 86.)

	County	Affected alive aged 10—49, 1945 (1)	Size gen. pop. whole county (2)	Aged 10—49, 1945. Birth regions (3)	Average heterozygote frequency whole county: min. value (4)		Average heterozygote frequency whole county: max. value (5)		Heterozygote-frequency in birth regions (6)		Pop. in the birth regions new civil divisions, as a proportion of the whole county, for: Affected alive aged 10—49, 1945 (7)	All affected in the material (8)	The 210 parents of all affected (9)	The same, based on old civil divisions, for affected alive aged 10—49, 1945 (10)
	Norrbotten	13	139,785	35,460	0.0096		0.0193		0.038		0.254	0.30	0.29	0.25
	Västerbotten	5	139,403	12,949	0.0036		0.0120		0.039		0.093	0.09	0.22	0.10
I	Västernorrland	6	165,268	15,351	0.0037	0.0046	0.0120	0.0142	0.040	0.042	0.093	0.17	0.28	0.09
	Jämtland	6	83,779	5,588	0.0044		0.0169		0.066		0.067	0.13	0.14	0.06
	Gävleborg	5	161,525	5,652	0.0021		0.0111		0.059		0.035	0.20	0.21	0.03
	Kopparberg	2	146,632	2,966	0.0011		0.0074		0.052		0.020	0.04	0.08	0.02
	Västmanland	1	108,583	34,287	0.0035		0.0061		0.011		0.316	0.33	0.02	0.26
	Uppsala	1	84,931	36,308	0.0043		0.0067		0.010		0.427	0.43	0.43	0.32
II	Stockholm (county)	4	188,570	46,019	0.0046	0.0034	0.0092	0.0071	0.019	0.007	0.244	0.25	0.02	0.19
	Stockholm (city)	1	411,465	411,465	0.0030		0.0031		0.003		1.000	1.00	1.00	1.00
	Örebro	4	136,709	41,840	0.0061		0.0108		0.020		0.306	0.31	0.02	0.27
	Södermanland	2	116,304	6,157	0.0019		0.0083		0.036		0.053	0.07	0.16	0.04
	Värmland	3	159,635	11,245	0.0023		0.0087		0.033		0.070	0.08	0.09	0.06
	Göteborg & Bohus	8	306,920	215,755	0.0084		0.0102		0.012		0.703	0.70	0.67	0.63
III	Skaraborg	5	140,259	11,004	0.0034	0.0048	0.0119	0.0099	0.043	0.016	0.078	0.09	0.13	0.03
	Älvsborg	4	200,300	36,566	0.0038		0.0089		0 021		0.183	0.23	0.11	0.16
	Halland	2	90,146	1,824	0.0013		0.0094		0.066		0.020	0.02	0.06	0.01
	Östergötland	4	194,808	54,537	0.0048		0.0091		0.017		0.280	0.32	0.30	0.24
	Jönköping	3	149,371	27,408	0.0039		0.0090		0.021		0.183	0.20	0.22	0.16
IV	Kalmar	6	133,230	25,376	0.0059	0.0043	0.0134	0.0113	0.031	0.025	0.190	0.19	0.13	0.02
	Kronoberg	2	88,274	4,673	0.0022		0.0095		0.041		0.053	0.07	0.09	0.03
	Blekinge	3	85,729	4,158	0.0026		0.0118		0.054		0.049	0.11	0.13	0.03
	Gotland	4	33,433	4,288	0.0078		0.0218		0.061		0.128	0.13	0.23	0.03
V	Kristianstad	9	145,646	14,237	0.0049	0.0052	0.0157	0.0109	0.050	0.014	0.098	0.22	0.15	0.07
	Malmöhus	5	323,886	158,119	0.0054		0.0079		0.011		0.488	0.56	0.55	0.44
Σ		108	3,934,591	1,223,232	0.0043		0.0105		0.014		0.311	0.34	0.32	0.28

aged 10—49 years, according to the »old» division into communes applying before 1950: column (10).

The new division into communes presumably gives more plausible figures for the population basis of the birth parishes than does the old division, even if objections can be raised to the use of either of them. Such a procedure is, however, the only feasible approach for obtaining even some estimate of the conditions.

The heterozygote frequency calculated according to the HARDY—WEINBERG law, approximately equal to $2\times$ the square root of the frequency of recessives in the actual birth regions of the affected, is given in column (6) of Table 26. Correction for the county of Norrbotten, assuming a mean coefficient of inbreeding of $\alpha=0.002$ (which cannot be regarded as altogether unplausible, *cf.* BÖÖK, 1948) would give a decrease in the heterozygote frequency calculated in this way from 0.038 to 0.035. However, as pointed out earlier, other sources of error may presumably be of a higher order of magnitude than any due to neglect of this correction. Moreover, for lower frequencies and lower values of α, the correction will be practically negligible.

The figures in column (6) for the birth regions in each county can presumably be regarded as, on the average, the highest for the partial populations in which the gene occurs. It is, in fact, reasonable to expect the disease to appear particularly in the population areas having the highest heterozygote frequency.

Using the figures in columns (3) and (6), a hypothetical estimation has been made of the *absolute number* of heterozygotes in the respective birth regions for the affected in the respective counties. Let us now make the assumption, which is, however, certainly not in agreement with the actual conditions, that no heterozygotes exist in the population of the county outside the birth regions of the recessives. If the calculated number of hypothetical heterozygotes is put in relation to the whole population of the county of corresponding age, the frequencies in column (4) are obtained. The average heterozygote frequency in each county as a whole can scarcely be anticipated to be lower than these »minimum» estimates, but in all probability to be considerably higher.

The number of recessives in each county, born within the stated period and alive on the date in question is nevertheless small, in certain counties there being only one living between the age of 10 and 49 years. Consequently, evaluation of the calculated frequencies must be made with the utmost caution. For the aforementioned five large geographic regions, we can summate the calculated number of hetero-

zygotes in the birth regions. This sum is divided by the population in the whole geographic region. We thus get a »minimum» heterozygote frequency for the whole region. These figures (weighted means) are recorded directly to the right of column (4).

The *over-all, or maximum, value* for the whole large geographic region is given to the right of column (5) and that for the corresponding county to the left in the same column. These figures are the same as those recorded in column (5) of Table 25 in the preceding section. They were obtained by expressing the number of recessives as a proportion of the whole population in the respective regions. Thus, the procedure was exactly the same as that used to obtain an over-all value of 0.01 for the heterozygote frequency in the whole country, by expressing the total 108 recessives as a proportion of the whole population of the country, aged 10 to 49 years at the time of the aforementioned census.

For the whole country, we obtain a minimum estimate of the heterozygote frequency of 0.0043 with the premise that heterozygotes are present only in the birth regions of the affected, and an over-all value of 0.0105. It seems probable that the true value lies between these values, probably closer to the higher one. As pointed out earlier, there is reason to assume that the hypothetical gene is fairly widely scattered over the whole country, even if its frequency naturally varies in different regions.

Columns (7) to (10) show, as related above, the population in the parishes of birth in the various parts of the material, expressed as proportions of the whole population. Comparison between the figures in columns (7) and (10) shows that the new division of communes did not lead to any great displacements for the present material.

Gotland, a flat island with an area of 3,100 square kilometers and a population of 42,000, is one of the exceptions. Before the reform, it was divided into 90 small communes, which were then combined into 12. However, the whole island probably functions as a *single* isolate, and it is scarcely possible to envisage any population-genetic barriers or isolate barriers of a geographic nature on it. The large number of small parishes existing before the reform were, in fact, to be found in relatively closely populated plains, containing no isolate barriers. This also applied to Öland, a similar island in the Baltic, the plains of Skåne (Malmöhus and Kristianstad counties), Östergötland and Västergötland (Skaraborg and Älvsborg counties) and the plains around Lake Mälaren. The existence of so many small parishes in these regions can be explained only against the historical background. They date from the introduction of Christianity into Sweden, which occurred first in these

TABLE 27. *Frequency of recessives (affected) and frequency of heterozygotes in rural and in urban districts, calculated under various assumptions.*

Area	Frequency of affected	Frequency of heterozygotes, whole country average values		Frequency of heterozygotes in birth areas of affected
		min.	max.	
Rural districts	0.000041	0.003	0.013	0.050
Urban districts, excl. Stockholm	0.000015	0.005	0.008	0.012
Urban districts, incl. Stockholm	0.000013	0.005	0.007	0.010

lowland regions, rich even at that time. From the point of view of modern population statistics, they can scarcely be considered of any importance. One can easily walk through five to ten such parishes or more in one day, in a tour of about 30 kilometers.

On basis of the birth parishes of the affected persons, we now make a frequency calculation for urban and rural districts (see Table 27). The over-all values for affected recessives seems to be two or three times as high in rural districts as in urban. Because of the high incidence of migration to and from the capital, Stockholm differs from the rest of the country from a point of view of population statistics.

In the rural districts, the hypothetical average heterozygote frequency can be estimated at 0.013; in th urban districts, the corresponding figure is 0.008. The frequencies are thus of practically the same order of magnitude. Let us assume that the heterozygotes are found only within the birth regions of the affected, and then estimate their absolute number in these regions in the rural and urban districts, respectively, using essentially the same principle as earlier. If then we express figures as a proportion of the whole population, we obtain a mean »minimum» value of 0.003 for the rural and 0.005 for the urban districts. As pointed out earlier, these »minimum» values are in all probability too low as an estimate of the »true» value in the population. In the rural districts, the population in the regions of birth of the 85 affected persons comprises about 0.15 of the whole population in the rural districts. The corresponding figures for the urban districts are 0.57 and 0.44, depending on whether or not Stockholm is included.

It is, however, immediately evident that the spread of the presumptive gene must be more extensive than the parishes of birth of the cases registered, the number of which is, of course, a function of the length

Fig. 4. Total 82 marriages of parents of the affected contracted during 1891—1936: distribution by county (listed from north to south) and year.
● denotes that both parents were born in the same county, ○——○ that they were born in different counties.

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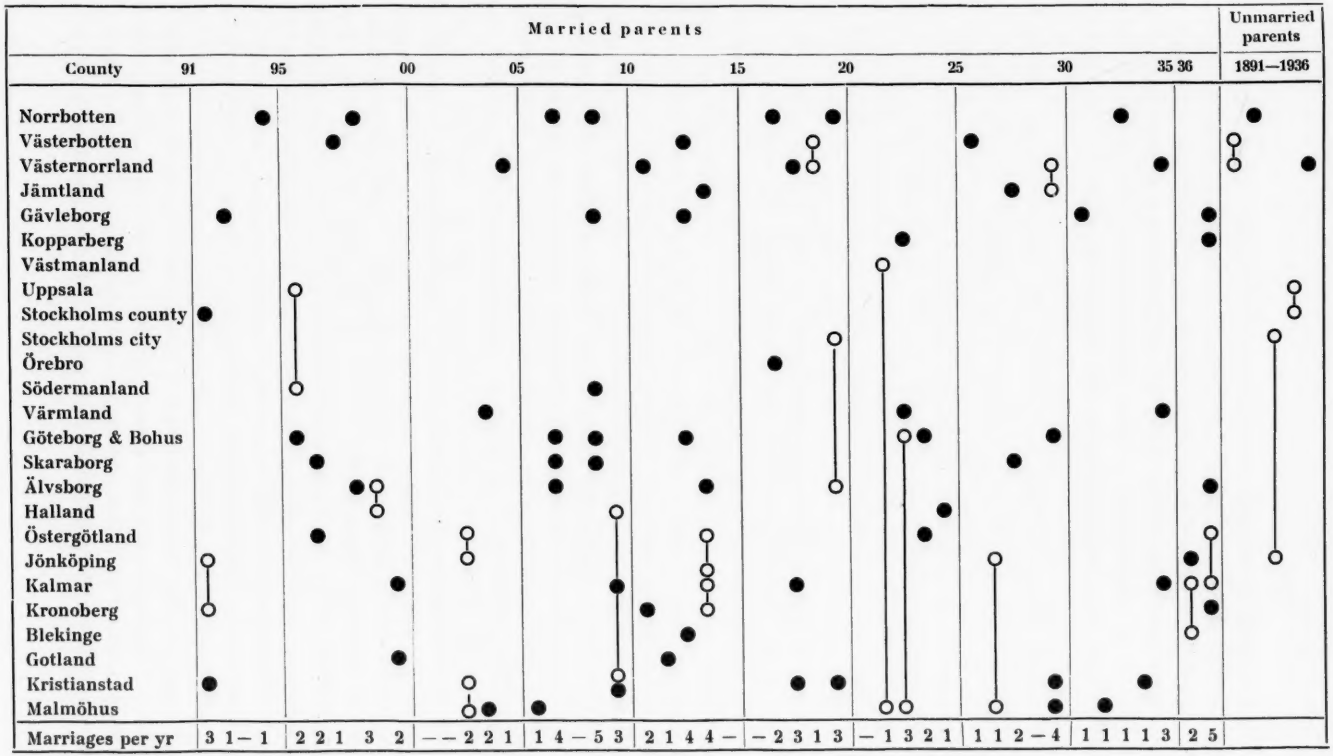

TABLE 28. *Number of marriages per year during 1891—1936, i. e. hypothetical heterozygote × heterozygote matings, with at least one affected child; observed frequency of years with 0, 1, 2, etc. marriages, with an average of 1.8 marriages a year, and expected frequency according to Law of small numbers.*

(See PEARSON, Tables for Statisticians and Biometricians, Part I, p. 113, Poisson distributions for $\overline{m}=1.8$ and $\overline{m}=1.1$.)

No. of marriages per year	Frequency		$\frac{(\tilde{m}-m)^2}{m}$	Frequency expected for $\overline{m}=1.1$	$\frac{(\tilde{m}-m)^2}{m}$
	Observed	Expected for $\overline{m}=1.8$			
0	8	7.6	0.0211	15.3	3.4830
1	15	13.7	0.1234	16.8	0.1929
2	10	12.3	0.4301	9.3	
3	7	7.4		3.4	
4	4	3.3	0.0290	0.9	6.1333
5	2	1.2		0.2	
6 — ω	—	0.5		0.0	
			$\chi^2=0.6036$		$\chi^2=9.8092$
			$n'=4$		$n'=3$
			$0.95<P<0.96$		$0.007<P<0.011$

of the registration period in the investigation. Had the registration period been very short, few cases would have been detected, resulting in a far smaller birth region. Similarly, a longer registration period could, at least theoretically, be expected to result in a larger birth region. This observation may appear superfluous, but it is made to prevent any misunderstanding.

The following may be of some interest in this connexion. In Fig. 4 on page 91, each marriage is recorded in the year it was contracted and the county of birth of the partners (parents). A dot indicated that both parents were born in the county in question, a circle that they were born in different counties. It can be inferred from the summation for each year at the foot of the diagram that the hypothetical heterozygote×heterozygote matings in the material during the period in question have a certain tendency to occur in series, as is commonly the case with rare events. The mean number of marriages per year during the 46 years is 1.8; for the first half of the period 1.9 and for the second half 1.7. The observed distribution over the 46 years of 0, 1, 2 . . . such matings is recorded in Table 28. It is reasonable to assume that it should follow a random distribution according to the law of small numbers.

Let us consider the following. Assume that the heterozygotes are largely spread over the whole country, with an average frequency of about 0.01, as calculated in various ways in the aforegoing. The average number of heterozygote×heterozygote matings out of all marriages contracted in the country can then be expected to be 0.0001. It could be inferred from Table 21 (p. 64) that the number of marriages with at least one child contracted between 1891 and 1936 could be estimated at a fictitious figure of 1,461,889 for the whole population. Of these, $1/46\times\times 0.0001\times 1{,}461{,}889=3.2$ per year could be expected, according to the hypothesis, to be heterozygote×heterozygote matings. It could also be deduced from Table 21 that $82/145=0.57$ of these, *i. e.*, 1.8 per year, could be expected to have at least one affected child, or the same figure as that actually observed. The agreement is not surprising in view of the fact that the calculations in Table 21 gave a heterozygote frequency of about 0.01.

We now once more set up the hypothesis that heterozygotes are found in the country only in the birth regions of the affected, amounting to about 31 per cent of the population according to the calculations in column (7) of Table 26 (p. 87). We have calculated, in this birth region, a mean frequency of heterozygote×heterozygote matings of $0.014\times 0.014=0.000196$ (*cf.* column (6), Table 26). We make the approximation that 31 per cent of the marriages contracted in the country took place in the population region in question, and correct as earlier for heterozygote×heterozygote matings with at least one child but no affected child. We can then expect an average of $0.31\times 1/46\times\times 0.000196\times 1{,}461{,}889\times 0.57=1.1$ heterozygote×heterozygote matings per year in the whole country with at least one affected child.

With the help of PEARSON's Tables for Statisticians and Biometricians (Part I, p. 113) the Poisson distributions (random distributions according to the law of small numbers), with $\bar{m}=1.8$ and $\bar{m}=1.1$, have been calculated for the expected number per year of matings during the calculated for the expected number per year of the matings during the 46 years of the observation period. Table 28 shows both the observed series and the expected series according to the two hypotheses. It is evident from the χ^2 analysis that the first series is in good agreement with the observed data, whereas this does not apply to the second series.

Naturally, this cannot be taken as an indication that the hypothetical heterozygotes are *evenly distributed* over the country. This would be unplausible, in view of the relative rarity of the gene, among other matters. It was apparent from column (5) in Table 25 that the frequency

varied in different parts of the country, being highest in the north and south, and lowest in the densely populated, probably most fluctuating population region in the middle of Sweden. It can nevertheless be pointed out that reasons exist for being somewhat sceptical regarding the assertion that heterozygotes occur only in a small part of the population and are entirely lacking in the rest of it.

On the basis of the discussions and of the numerical data given in this section, the following hypothesis may be put forward. The »true» value for the frequency of heterozygotes in the whole country can presumably be estimated as being perhaps lower but nevertheless of the same order of magnitude as the calculated over-all value of about 1 per cent for the whole population. The occurrence of the disease, widespread over the whole country, as well as the aforegoing calculations, do not, however, lend support to the claim that the »true» value comprises only a fraction of this figure.

The conditions appear to be similar in juvenile amaurotic idiocy, which has approximately the same frequency in the country as the form of disease now under discussion. SJÖGREN (1931), in the same way as here, calculated an over-all value of about 1 per cent of heterozygotes. This is presumably closer to the »true» value than DAHLBERG's assertion, based on a model af the genetic-statistical structure of the population constructed by him, that it is only a fraction of this value. It seems likely that DUNN's model would far more closely correspond to the actual conditions.

The following repetition can be made to sum up. Theoretically, two hypothetical models of the conditions can be constructed. According to one of them, the presumptive gene occurs in certain partial populations scattered over the whole country and is entirely lacking in the rest of the population. According to the other model, no such sharp delimitation exists, but the gene is more evenly distributed among the population in the whole country, although with a higher frequency in certain regions, so-called frequency peaks. From these »maximum» areas, the frequency falls continuously in all directions to lower values, and may even approach zero in certain larger or smaller areas, after which it again rises to other peaks. Even if, through genetic drift, it can conceivably disappear entirely for a time in small partial populations and regions, it seems feasible to infer that it can, sooner or later, reappear in such a region by »infiltration» from outside, through the gene flow. It does not seem unreasonable to believe that such local maxima and minima could,

in the long run, be evened out and be displaced in both space and time for a human population.

The first of these models is perhaps more compatible with the conditions probably applying a century or more ago. According to many authors, there were then more rigid isolate barriers, not only of a social but especially of a geographic nature. Owing to the breaking down of the isolate barriers that has occurred at an accelerated rate during at least the past 100 years, a stronger gene flow with a levelling effect can be assumed to have taken place in the whole country. During the past 60 or 70 years concerned in this investigation, the latter, less rigid model outlined above is presumably in better agreement with the true conditions.

If figures confined to migration to and from various geographic partial populations are used as a basis for investigation of the population movement from a genetic-statistical viewpoint, only an approximate idea, and in certain cases perhaps an entirely distorted one, of the true course of events can be obtained. A more correct idea is obtained if the *marriages* contracted during a certain period and in certain areas are used as a basis for the calculations, and the geographic origin of the respective partners is investigated.

The 105 families in the material, in which the sibships of the affected are denoted as generation I, are represented in generation IV, the parents of the grandparents, by 420 pairs of matings, *i. e.*, 840 ancestors. Reference is made to Table 23 (p. 68). Of the pairs belonging to generation IV for which exact data regarding the parish of birth of *both* partners were available, 270 pairs mated with the oldest and the youngest partner born during the period 1750—1829, and 118 pairs with the youngest partner born during the period 1830—1874. During the former period, mating between partners from different parishes occurred in 49 per cent

	No. of pairs	Pairs with partners from different parishes	Pairs with partners from different counties
		Per cent	Per cent
1750—1829			
North Sweden	110	38	5
South Sweden	160	56	15
Total	270	49	11
1830—1874			
North Sweden	50	28	10
South Sweden	68	63	9
Total	118	48	9

of the pairs, and from different counties in 11 per cent. The corresponding figures for the latter period are 48 and 9 per cent, respectively.

If the material is divided into two parts, *i. e.*, the northernmost 43 families comprising the whole of Norrland and the counties of Värmland and Kopparberg, and the 62 families south of this region, the conditions are as shown in the tabulation on p. 95.

The following tabulation is by way of comparison between the generations. It should be recalled that generation II denotes the parents of the affected.

	No. of pairs	Pairs with partners from different	
		parishes	counties
		Per cent	Per cent
Generation IV	388	49	11
» III	200	49	15
» II	105	62	23

The above figures seem to be remarkably high, at any rate for the oldest generation (IV). Moreover, for generations III and IV, they are presumably minimum figures. In the majority of pairs in which the parish of birth of one of the partners was known but not of the other, the latter was, with a high degree of probability, born in another parish. If these are also included in the calculations, the frequency of pairs of matings with partners from different parishes will be still higher.

There is presumably no reason to assume a higher frequency of migration among the ancestors of the affected recessives in this investigation than in the general population of that time. In view of the high incidence of consanguineous marriages in the present material, it seems more likely that the opposite was the case.[1] Obviously, no definite state-

[1] This should apply in particular to the ancestors in southern Sweden. During the 17th and 18th centuries, there was some influx of immigrants and colonists from Finland in the ancestors in the north of the country. This applies especially to the families belonging to the family complexes *A*—*D* and *R* in the four northernmost counties. It is known that there was a greater frequency of migration among these colonists than among the native population, the Swedes. They sometimes cultivated a homestead, failed after a varying period, and tried again in another place. In addition to these farming Finnish colonists, who seemed soon to have been assimilated into the rest of the resident population, there was another group of Finnish immigrants, the so-called forest Finns. They were chiefly engaged in forestry and hunting, and moved from one place to another to a far greater extent. Only the

ment can now be made on this matter. One of the most urgent tasks of population genetics today seems to be to ascertain factual data, which can serve as a concrete basis for the theoretical calculations and, from the point of view of population genetics, provide us with models to work with that correspond approximately to the actual conditions.

The aforegoing figures can obviously be accepted only with due reservation. They nevertheless seem to give grounds for some adjustment in the fairly definite view held in some quarters that the population in earlier times was divided into partial populations with relatively sharp isolate barriers. In view of the power of words over thought there is, in fact, reason to question whether the term »isolate» is altogether appropriate in this connexion. Racial barriers and national frontiers can suitably be denoted as isolate barriers. But the designation is presumably less adequate as far as the areas dividing a large population into partial populations is concerned. For, what can reasonably be regarded as separating, for instance, two areas are zones across which there is a sparser gene exchange than within the areas in question. But they can by no means be denoted as mutually »isolated». The term quasi-isolates (SNYDER, 1951) is more adequate.

DAHLBERG, who was one of the pioneers in the field of theoretical population genetics, and who has made most valuable contributions to its development, wrote as follows (1943, p. 124):

. »Die Isolatgrenzen besitzen u. a. deswegen Interesse, weil sie erklären, warum man schwere, seltene, rezessiv erbliche Krankheiten *in abgelegenen und abgegrenzten Dörfern* vorfindet. Um dies zu verstehen, muss man sich nur Folgendes überlegen. Entsteht eine Mutation in der Bevölkerung eines Bestimmten Isolates und breitet sie sich hauptsächlich nur dort aus, (aber kaum ausserhalb des Isolates), so ist die Wahrscheinlichkeit dafür, dass die Anlage in doppelter Dosis zusammentreffen wird, grösser, wenn das Isolat klein ist, als wenn das Isolat gross ist. In einem kleinen abgelegenen Dorf mit schlechten Kommunikationen sind die Verhältnisse für das Auftreten von Krankheiten dieser Art günstig. In grossen Isolaten, z. B. in einer Grosstadt, ist hingegen die Aussicht, dass eine solche Anlage sich manifestieren wird, klein. Aus diesem Grunde *findet man schwere Nervenkrankheiten, Idiotieformen und ähnliches in Dörfern, die weit abgelegenen sind und*

former group seems to be represented among the ancestors in the present material. The native Swedish population was somewhat inimically disposed to the Finnish immigrants, particularly the so-called forest Finns. This is borne out by numerous records of the courts of law (*e. g.* GOTHE, 1948, p. 162).

schlechte Kommunikationen besitzen.»[1] (The italics in both places are mine.)

This statement seems to me to be an expression of a too rigid concept of isolate barriers and implies an isolate theory driven to extremes.

Let us consider first that we can agree on a serviceable definition of what is meant by »a remote village with poor communications». But even so, in such a country as Sweden, the number of villages thus defined must be relatively small, and the total population in them a fairly inconsiderable proportion of the whole population. This explains why, in a representatively investigated material, the overwhelming majority of »schwere Nervenkrankheiten, Idiotieformen und ähnliches» do not derive from »remote villages with poor communications», but from population areas of a different nature. If, in a study of rare recessive traits, the investigation was confined to material derived from »remote villages», the material to be studied would be very small.

It must, however, be pointed out that DAHLBERG stressed (1943, p. 117) that the isolate concept constitutes a schematization of the situation. He wrote:

»Streng genommen fallen die Isolate für zwei Personen niemals vollständig zusammen und das Isolat für gewisse Personen geht allmählich in der Population auf, ohne dass man immer von scharfen Grenzen sprechen kann.» (Translation: »Strictly speaking, isolates never coincide completely for two persons, and for certain persons the isolate is gradually assimilated into the population, without one always being able to speak of sharp borderlines»).

He emphasized the consequence of geographic boundaries, and continued:

»Eine Gruppe von Personen, die nahe zueinander wohnen, hat indessen im grossen und ganzen ein gemeinsames Isolat. Zwischen den

[1] Translation of the quotation: »One of the reasons for which the isolate barriers are therefore of interest is that they explain why severe, rare, recessive inherited diseases are found *in remote and circumscribed* villages. In order to understand this, the following deliberation must be made. If a mutation occurs in the population belonging to a distinct isolate, and spreads itself mainly there (but scarcely beyond the isolate), the probability of the trait appearing in a double dose is greater if the isolate is small than if the isolate is large. In a small, remote village with poor communications, the conditions are favourable for the appearance of diseases of this kind. In large isolates, *e. g.* in a city, the likelihood of such a trait becoming manifested is, on the contrary, small. For this reason, *severe nervous diseases, forms of idiocy and the like are found in villages that are remote and have poor communications.*» (The italics in both places are mine.)

Isolaten der verschiedenen Personen sind mit anderen Worten die Unterschiede unbedeutend.» (Translation: »A group of persons living close to each other have, however, by and large, a common isolate. In other words, the differences between the isolates of different persons are inappreciable»).

It may be suggested that the term »range of choice», for example, is more adequate in this connexion than the term »isolate», which implies a number of other factors. One must agree entirely with DAHLBERG that the »ranges of choice» (»isolates») for two persons never coincide »streng genommen», not least for psychological reasons. Moreover, it is by no means certain that a group of persons living in close proximity »im grossen und ganzen» have a common »range of choice» (or »isolate»). In fact, it may well be that, on psychological grounds, an individual with a certain personality type is able to circulate only within a very limited »range of choice». Others, living or born in the same place, but having a different mental structure, perhaps circulate in a considerably larger and wider range, wider in the geographic sense as well. If this is actually the case, the proportions between these groups, which function differently from a point of view of population genetics, may be such that the above generalization is inadmissible. A basis for rational and serviceable mathematical calculations can perhaps be provided only by a social-statistical and sociologic field investigation of the actual mating conditions applying in the different partial populations (isolates in this sense).

The fact that extremely rare genetic recessive diseases, some of which may be the result of relatively new mutations — *cf.* KOSTMAN (1956) — are found in small local areas is fairly self-evident. The probability that the trait — unless it is lost through genetic drift — will first appear in a double dose at the »place of mutation» is naturally greater than that it would appear at a greater distance after migration from the place of origin. This should obviously apply even if the population region in question is not markedly »isolated».

Summary

In earlier sections, calculations were made of an over-all value of the heterozygote frequency in the whole country and in its different parts. The condition for such a calculation is a panmictic population in equilibrium.

In this section, calculations are made under certain hypothetical assumptions. The frequency calculations are not based on the whole population, but on the partial populations (parishes) in which the affected individuals (homozygotes) are born. Separate calculations are made for rural and for urban districts. The hypothetical assumption is made that heterozygotes do not occur outside the aforementioned birth regions. This assumption is certainly not in agreement with the actual conditions. However, the number of heterozygotes calculated in this way are put in relation to the whole population. The figures obtained can be regarded as minimum estimates of the »true values» of the heterozygote frequency in the population.

Reasons seem to exist to challenge the validity of the statement that the »true value» comprises only a small fraction of the over-all value, *i. e.*, the maximum value calculated in an earlier section. It does not even seem improbable that the »true value» lies closer to this than to the aforementioned minimum value.

The term »isolate» is discussed, and some criticisms are raised to its too rigid application in constructing theories in population genetics, in any event for the population of Sweden. An investigation is made of the mating conditions of ancestors of the affected persons. In this material, the frequency of matings between partners from different partial populations is found to be remarkably high in earlier generations. These conditions are discussed.

7. *Mortality, Fertility and Mutation Frequency*

The 175 affected individuals, who had all passed one year of age, had 303 unaffected sibs, who had also survived this age. These 478 sibs had 15 sibs who died before one year of age. If one death during parturition and one on the day of birth are disregarded, the mortality during the first year of life in these sibships is $13/491 = 0.026 \pm 0.007$. There is thus no increased infant mortality as compared to that in the general population.

Of the 175 affected, 17 males and 21 females were dead on Dec. 31, 1946. Tuberculosis was the chief cause of death (6 males and 9 females), *i. e.*, 40 per cent of all deaths. The cause of death, age at death in the individual cases are shown in Appendix 6 (p. 128).

The material is definitely too small to permit any exact determination of the mortality as compared to that in the general population. It is, however, possible for an approximate comparison to be made, for

general information, with the help of a method suggested by SJÖGREN and LARSSON (1949, p. 38). The calculation has been hade only on the cases admitted to Tomteboda Institute. The starting point of the observation period in the individual case was the age at entry to the Institute (Elementary School), the average age being 10 to 12 years. The end of the observation period was Dec. 31, 1946. Altogether 124 pupils, 59 males and 65 females, were registered at the Institute, including 4 registered before 1897. Of these, 6 males and 14 females had died up to and including 1946.

Using the same designations as SJÖGREN and LARSSON, the observed number of years survived by male pupils is R ♂=1,180, and by females R ♀ =1,120.

The expected number of years survived, on the basis of the mortality in the general population for the periods 1901—1910 and 1936—1940, respectively, are for male pupils P′ ♂=1,134 and P″ ♂=1,269, respectively. For female pupils, we get P′ ♀=1,477 and P″ ♀=1,658, respectively, as the expected survival period in years.

R ♂ as a percentage of P′ ♂ and P″ ♂=104 and 93, respectively.

R ♀ as a percentage of P′ ♀ and P″ ♀=76 and 68, respectively.

The percentage figures may indicate a mortality in the male pupils corresponding to that in the general population. For the female pupils, an increased mortality seems to be present in this sample. Owing to the small size of the material, no general conclusions are, however, permissible.

Table 29 shows the number of affected males and females >15 years of age alive on Dec. 31, 1946, both alone and including those >15 years of age dead before this date. The observed and expected number of unmarried, according to the conditions in the general population, give a statistically significant lower marriage frequency for affected males as well as females. The expected number of married males and females is then $0.56\times65+0.62\times68=78$, with a very approximative average (at a low estimate) of 2 children per marriage, the number of expected children thus being 156.

The observed number of married is 29, and the observed number of children is 34. The youngest is 2 years old and 20 are over 15 years old. We have 13 sibships, *i. e.*, marriages with children, 5 consisting of 1 child, 5 of 2, 1 of 3, 1 of 7 and 1 of 9 children. Furthermore, we have one child born out of wedlock. They are together 17 males and 18 females.

The expected approximate number of children of 156, and the ob-

TABLE 29. *The observed frequency of unmarried individuals among the affected. The expected frequency standardized according to age and general population of Sweden 1945.*

(Statistical Year-Book of Sweden 1952, Table 18, p. 16. Figures in brackets are percentages.)

	Men			Women		
	No. of affected	Unmarried		No. of affected	Unmarried	
		Exp.	Obs.		Exp.	Obs.
Alive 1946 > 15 years of age	55	22.64 (41)	38 (69)	54	20.50 (38)	43 (80)
Alive 1946 > 15 years + dead > 15 years of age	65	28.67 (44 ± 6)	48 (74)	68	25.95 (38 ± 6)	56 (82)

served number of 34, give a value for the relative fertility of individuals homozygous for the hypothetical gene of $f=0.23$.

Let us assume a very high mortality in the affected before the age of 15. Let us also make the improbable assumption that all the 13 who died before 15 years of age, if unaffected, whould have reached a marriageable age and remained unmarried. This would only decrease the value of f to 0.21.

The mortality of the 303 unaffected sibs of the affected who had passed one year of age has been calculated. Here, this age was used as the beginning of the observation period. The »exact duration method» (*cf.* ALSTRÖM, 1942, p. 40 and »the method of the calculated number of deaths», *ibid.*, p. 47) has been used.

	No. of Deaths	
	Expected	Observed
Unaffected male sibs	29.5	29
Unaffected female sibs	21.0	15
Total	50.5	44

The sample is small but, as may be inferred from the above tabulation, there is no reason to expect a mortality in the unaffected sibs of the affected persons differing from that in the general population. The majority of the sibs, approximately $^2/_3$, can be expected to be heterozygotes. The fertility of the unaffected sibs has not been calculated.

The impression is, however, that there is presumably no difference from that in the general population, or at any rate no decisive one.

As NEEL and SCHULL, among others, have justifiably stressed, all estimates of the rate of mutation of recessive genes must be regarded as highly tentative. An estimate can, however, be made according to the formula

$$m = (1 - f) \cdot r^2$$

in which f is the relative fertility of the recessive affected individuals, and r^2 their frequency in the general population. In this case, we get an approximate value of $m = 0.77 \cdot 0.00003 = 2.3 \cdot 10^{-5}$. This is probably a minimum value, for the following reasons. There may, in the long run, be a higher mortality in the homozygotes than that assumed here. Despite the relatively strict organization for the blind in Sweden, it is naturally possible that a certain number of cases have not been registered, and have been missed in this way. It is improbable that the present day population of Sweden is in genetic equilibrium. We must presumably count on a continuous decrease in the incidence of consanguineous marriages in the general population. As NEEL and SCHULL (1954, p. 143) have pointed out, a mutation rate estimated on the frequency of the homozygotes will then be too low. As far as the heterozygotes are concerned, there seems to be no reason to anticipate any decrease in their viability.

Another possible pitfall may be that we are not, in fact, dealing with a genetically homogeneous disease, but with a trait caused by mutations at several different gene loci. This is a difficulty inherent in all human genetic investigations, in which the possibility of definite proof, such as crossing experiments, is lacking. It nevertheless seems feasible to set up the hypothesis that at least the majority of the cases in question here represent a homogeneous form of disease.

Summary

The mortality below one year of age in the sibships of the affected (the affected and their unaffected sibs collectively) does not seem to be higher than the corresponding figure in the general population. The mortality seems to be increased in the affected females but not in the affected males. The small size of the material does not, however, permit any definite conclusions. The mortality does not appear to be increased in the unaffected sibs; this applies to both the males and the females.

The marriage frequency and the fertility of the affected persons are greatly reduced in comparison with the general population.

With all due reservations, an attempt has been made to determine the frequency of mutation in the hypothetical form of disease. Certain sources of error are listed.

8. *Frequency of Oligophrenia, Psychoses, Epilepsy and other Diseases in the Families of the Affected Persons*

An account of the cases of severe oligophrenia, psychoses and other diseases in the families of the affected is given in Appendix 5 (p. 125) and Table 30.

In the *175 affected*, there were 5 cases, *i. e.*, 2.9±1.3 per cent, of

TABLE 30. *Incidence of psychosis and some other diseases in the affected individuals and their relatives (cf. Appendix 5).*

175 Affected	
Severe oligophrenia	3
Do.+endocrine dysfunction+epilepsy	1
Do.+epilepsy	1
Imbecility	1
Dullness	3
Schizophrenia	4
Manic-depressive psychosis	1
Epilepsy; mentally healthy	2
Progressive organic dementia+epilepsy	2
Diabetes+epilepsy	1
Deaf-mutism	1
Impaired hearing	1
303 Unaffected Sibs (unimpaired vision)	
Severe oligophrenia	2
Imbecilitas	1
Organic dementia	1
Schizophrenia	2
210 Parents	
Dullness	1
Schizophrenia	2
Psychosis due to cerebral arteriosclerosis	1
Deaf-mutism	2
Impaired hearing	1
»Retinochoroiditis»	1

severe oligophrenia. In one of these cases endocrine dysfunction and epilepsy were also present; in another there was concomitant severe rachitis, congenital hydrocephalus and epilepsy. All five had affected sibs with normal intelligence (*cf.* Appendix 5, p. 125). In one case the parents were first cousins; in another they were related 5—5. Oligophrenia of milder degree (within physiologic limits) was present in 4 cases: imbecility in 1 case and dullness in 3.

In two cases, epilepsy and progressive organic-neurologic dementia were present. In one case the onset was before 7 years of age, in the other at 8 years of age.

Uncomplicated epilepsy was present in two cases; both were unaffected mentally. In one, the duration was from 15 to 24 years of age, with no seizures during the subsequent 10 years. In the other, the onset was at 16 years of age, with about 1 to 2 seizures a month. Diabetes was present in one case since 8 years of age, and necessitated insulin therapy. Occasional epileptic seizures appeared at the age of 11; they seemed to be associated with difficulties in insulin adjustment. The patient was mentally healthy. In 4 cases there was schizophrenia, and in 1 case manic-depressive psychosis.

One affected person was deaf and dumb following epidemic meningitis at one year of age. One had impaired hearing after 44 years of age; the hearing had earlier been normal. Thus, in these cases, there was no such correlation between impaired vision and impaired hearing as has occasionally been stated in the literature to exist in retinitis pigmentosa, for example. In one case, F. 17, both parents were deaf-mutes. In one of them the condition was congenital, in the other it had appeared after an illness in early childhood and was thus not congenital. Both had unimpaired sight. They had three children, one of whom was affected; all three had normal hearing.

In the *303 unaffected sibs*, there were 2 cases, *i. e.*, 0.7 ± 0.5 per cent, of severe oligophrenia. In one case, the three affected sibs were intellectually and mentally normal. In the other case, the affected sib had epilepsy since 16 years of age, but was otherwise intellectually and mentally unaffected. There was one case of progressive organic dementia after meningo-encephalitis at an early age. One case can be regarded as a feeble-minded to imbecile within physiologic limits. A schizophrenic psychosis was present in two cases.

It is true that the frequency of such disorders as oligophrenia and psychosis in the affected did not differ significantly from that in the general population (*cf.* SJÖGREN, 1948, LARSSON and SJÖGREN, 1954)

or from that in the unaffected sibs. The fact that a few more cases were recorded in the affected sibs than in the unaffected nevertheless seems to me to be remarkable. It may be due to chance, but another plausible explanation is that the affected sibs have been more thoroughly investigated than the unaffected, and that this may imply some bias. The observed frequencies of the disorders in question are, however, small and it is evident that no correlation exists between them and the disease of the eye studied here.

Of the *210 parents of the affected*, 2 exhibited schizophrenia and one a psychosis on an arteriosclerotic basis. One is denoted as feeble-minded with certain difficulties in social adjustment. One father had impaired hearing but was not deaf. His two sibs had normal hearing, as did his three children, two of whom were affected. In one case both parents were deaf-mute (*vide supra*). The father's four sibs and the mother's six sibs all had normal hearing, as did their three children, one of whom was affected. The deaf-mute parents had attended the same school for the deaf and dumb.

In one case, F. 34, the father was also affected, *i. e.*, suffered from congenital retinochoroiditis. He belonged to F. 33 and was married to a normally-sighted woman from his home district. They are related 5—5. His affected sister, F. 33 d, is also married and has two normal children. The family belongs to the *De* complex.

The *35 children of the affected* belong to 14 sibships. In two cases, F. 11 b and F. 33 b, marriage has resulted in an affected child. One is F. 34 a, son of F. 33 b, mentioned several times. Regarding the son of F. 11 b, see p. 83. In the remaining sibships, all the children are normally sighted. The sibships have been thoroughly investigated, and no mental or physical defects occur in this small sample. One son is a non-commissioned officer in the Air Force; several have driving licenses. None of those who has reached school age (except the two mentioned above) has any impairment of vision or other difficulties at school.

Summary

It is apparent from the aforegoing that the disease of the eye studied in the present investigation does not seem to be combined with disorders of a neurologic or psychiatric nature. When such occur, it is justified to regard them as random complications. It can be stressed in particular that no genetically determined combination with deafness is present.

General Summary

(1) Since 1897, Tomteboda Institute for the Blind in Stockholm has been the central institute and only elementary school in Sweden for the education of mentally normal blind children. In this year, a law was passed enforcing compulsory education of blind children and those with defective sight.

(2) The material for the present investigation was assembled from Tomteboda Institute, and comprises about 10 per cent of the pupils admitted to its elementary school during the 1897—1948 period.

(3) Initially, the basic material consisted only of cases with the diagnosis congenital »retinochoroiditis» without known cause. The proband criteria were subsequently extended to include cases with the diagnosis of amaurosis or amblyopia congenita without known cause. The reason was that such cases were found in the sibships of persons with the aforementioned diagnosis, and that some of them later exhibited such fundus changes, and were then diagnosed as »retinochoroiditis». Altogether 90 proband families were traced from the 1897—1948 period.

(4) An additional 15 families were traced through the proband families. Some of them had affected members admitted to Tomteboda Institute before 1897 and others had affected members who, despite the law, had not been educated at Tomteboda. The material from the early part of the period also contains a few secondary cases, mainly in the proband families, with amaurosis congenita and the diagnosis optic nerve atrophy without known cause. A survey of the basic material is given in Tables 1 and 2.

(5) The total 105 families (90 proband and 15 secondary families) contain 175 affected sibs, of whom 48 per cent are males. They have 303 unaffected sibs. The calculations are based on those who survived one year of age; 15 died before reaching this age.

(6) It is evident from Table 3 that most of the affected persons underwent repeated examinations at very varying ages. Examination was made before 15 years of age in 152 cases. Of the remaining 23, 10 were

examined later. The cases in which examination was made after 15 years of age are shown in Table 4; including the 10 just mentioned they amount to 137.

(7) Table 6 shows that, in the persons examined before 15 years of age, the diagnosis was »retinochoroiditis» in 61 per cent, amblyopia congenita in 28 per cent and optic nerve atrophy in 10 per cent. One per cent (2 cases) exhibited cataract on admission to the Institute.

(8) A conception of the clinical development of this familial condition is obtained by grouping the affected persons by age. The material is therefore divided into 3 age groups: under 15 years, 15—45 years, and over 45 years at the time of examination (see Tables 5 and 6). These groups contain 152 (153), 101 and 42 cases, respectively.

The incidence of cases with so-called retinochoroidal changes increases from about 60 per cent in the youngest age group to about 80 per cent in the oldest. The latter figure should probably be even higher, since there is reason to assume that such changes are present in at least some of the cases with dense bilateral cataract. This question is discussed (*cf.* point 12). Cases without demonstrable fundus changes (those with so-called amblyopia congenita) show a corresponding decrease, *i. e.*, from 28 per cent, via 23 per cent in the middle age group, to 5 per cent in the oldest. It is highly probable that, if systematic investigations could have been made soon after birth, the frequency of cases without visible fundus changes would have been higher than on starting school to which age the figures in the youngest age group refer.

(9) The »retinochoroidal» changes were variable and uncharacteristic. It is stressed that the term »retinochoroiditis» is obviously inadequate, since the changes are not of an inflammatory nature. When any changes were present in young patients, they sometimes consisted of minute, round, pale spots that were scarcely visible, scattered in the periphery of the fundus. Sometimes very small round or irregular, black pigmented spots, often sparsely scattered, were present in the same location. The pigmentation seems to spread extremely slowly during youth. After some years, round or irregular pigmentations of varying size predominate.

Widespread retinochoroid atrophy with fairly large, irregular, black or slate-grey patches was seen only in the most long-standing cases, and in some of them white areas of sclera, with atrophy of both the retina and choroid, were visible. In a few cases, pigmentations resembling bone corpuscles were observed, in addition to the other changes, which

always predominated. Alterations in the central part of the fundus were rarely present.

(10) Some atrophy of the disc and a moderate degree of narrowing of the vessels are often found. When these papillary and vascular changes are present, they are not nearly as conspicuous as in cases of retinitis pigmentosa with equally severe impairment of sight. Moreover, it can be pointed out that of the persons under 15 years old without evident fundus changes, 21 per cent were completely blind and a further 12 per cent had only some perception of light.

Cataract and keratoconus are two conditions with a strikingly high incidence in these patients (see Table 6). They are often present concurrently (Table 3).

(11) In the youngest age group, cataract is found in 10 per cent; it is generally incipient and of small punctate shape or in the form of a few »riders». Only two secondary cases are exceptions; when they started school they already had dense cataract preventing inspection of the fundus.

The frequency of cataract is found to increase with age. In the earlier part of the 15—45 years group it was present in 20 per cent, and in the later part of the same group in about 30 per cent. In the highest age group (over 45 years) almost three-fourths of those investigated had cataract. Not only did cataract become more common, but its size and density increased with age, making it extremely difficult or even impossible to inspect the fundus. Operation was performed in two such cases, and disclosed advanced. chronic »retinochoroidal» changes and atrophy. Usually, cataract was not uniformly developed in both eyes.

(12) Keratoconus was present in a few per cent of cases in the youngest age group. It is also found to increase with age, its frequency in the middle age group being the same as that of cataract. In the highest age group, it is recorded in about one-third of the cases. The same conditions apply in keratoconus as in cataract. When it is present in the younger age groups, it is usually at an early stage, but develops progressively with age, often combined with corneal opacities and keratomalacia.

(13) All these various and apparently highly heterogeneous conditions are represented in one and the same family and in the same family complex, and even in a single sibship. Their development could also be followed in several individual cases observed during a long period (see survey in Table 3). There may, in fact, be a variability (a) with age in the individual case, (b) between members of the same

family, (c) between families both in the same family complex and related families, and (d) between families outside the family complex and not related.

(14) All the affected persons had impaired vision observed soon after birth or during the first year of life. There is reason to assume that it was congenital. In the persons with some sight when first observed, a very slow deterioration of vision seems to occur. In the youngest age group, 47 per cent of those in whom the vision was estimated had total amaurosis or perception of light only. In the highest age group, this applied to three-fourths of the cases (Table 8). The class with the best vision, 0.1 and more, comprised 11 per cent of the youngest age group; this figure fell in the highest age group to 2 per cent of the cases examined. With respect to the variability, the same conditions apply as those listed under point 13. In no case was anything observed that could be interpreted as tube vision, nor could any progressive limitation of the visual field be noted. For pupillary reactions see p. 34.

(15) An almost constant phenomenon was the occurrence of irregular or nystagmus-like eye movements, which made it difficult or impossible to photograph the eye-grounds. These eye movements, and an incapacity for central fixation, were particularly apparent in the least advanced cases with the best vision.

(16) Electroretinographic examinations could be performed in 62 cases, most of them belonging to the two higher age groups. The ERG was extinguished in 92 per cent and subnormal or nomal in 8 per cent (5 cases). Of these a flicker ERG was recorded in 4 cases, and showed a loss of cone function in two of them (F. 15 a and F. 16 a). These cases belong to a large family complex (*A*—*D*) with other cases investigated showing an extinguished ERG. One case (F. 13 a) showed very low values for both rod and cone function. In another case (F. 50 a) there was a decrease in the flicker potentials at high light intensities. F. 50 a was related to the sibship F. 85. An ERG was recorded in one of the latter and was extinguished. In another case (F. 73 b), in which the ordinary ERG was extinguished, potentials were recorded on the flicker ERG at the highest light intensities only. (A report of the ERG investigations in these cases will be published by G. KARPE.)

(17) A Mendelian analysis with WEINBERG's proband method gives a frequency of affected in the proband families of 22.4 ± 2.0 per cent. Analysis with the method suggested by HOGBEN gives a deviation equal to the standard error above the expected value according to the hypothesis of monohybrid recessive autosomal inheritance.

(18) Further analysis with HALDANE's method gives a frequency of affected in the sibships of the whole material of 27.4 ± 2.5 per cent. Calculations on the proband families alone give the same value. The deviation may be assumed to be due to chance.

(19) Calculations of the frequency of affected in families of different size, using HALDANE's method, give throughout higher deviations from the expected 25 per cent for »smaller» families than for families of larger size (see Table 10). These may be random deviations, but the possible slight effect of a family-limiting factor of psychological nature is pointed out, analyzed and discussed.

(20) The 105 families are grouped according to the following viewpoints: (a) those in and outside the large family complexes, (b) those recorded in the later part of the investigation period, (c) their geographic origin. Calculations with HALDANE's method show that the present material seems to be fairly homogeneous with respect to the frequency values obtained for the affected persons and, hence, the mode of inheritance.

(21) In view of the law regarding compulsory education of blind children and of the organization of the blind in Sweden, the present material can be assumed to be fairly complete with respect to the trait in question.

Attempts are made to calculate the frequency of the trait, the hypothetical gene frequency, and the heterozygote frequency, assuming that we are dealing with a homogeneous, genetically determined form of disease. Estimates based on (a) those born between 1891 and 1938, alive on Dec. 31, 1945, (b) those born between 1891 and 1938, who survived one year of age, and (c) children born between 1918 and 1937, who reached school age show fairly good agreement. The frequency of the trait in the general population of Sweden can be estimated at about 3 in 100,000. According to the HARDY—WEINBERG law, the gene frequency can be estimated to be 5 to 6 in 1,000, and the heterozygote frequency about 1 per cent (Table 22). An »indirect» calculation is also made, based on marriages between the parents of the affected, contracted between 1891 and 1936. It is of interest to note that these calculations give about the same values as those just mentioned.

(22) A mean coefficient of inbreeding of $\alpha = 0.01$ is calculated, at a low estimate, to apply in the present material, *i. e.*, about 5 to 10 times higher than can be expected in the general population of Sweden. The frequency of a first-cousin relationship between the parents of the affected is 16.2 ± 3.6 per cent. The fact that due caution must be ob-

served in using WEINBERG's formula for estimating a hypothetical gene frequency is pointed out and discussed. It is, however, of interest that such an estimate is in good agreement with those given under point 21, *i. e.*, about 5 in 1,000 (see Table 24).

(23) An attempt is made to determine the geographic distribution of the trait. Sweden is divided into 25 large administrative regions, the capital (Stockholm) and 24 counties (Table 25, Fig. 1). The highest frequencies are found, in addition to in the island of Gotland in the Baltic, in the northernmost and the southernmost counties. Owing to the smallness of the figures, every reservation must be made in drawing conclusions as to the conditions in the individual counties. They have therefore been assembled into five large regions (Table 25). The highest frequencies are then found in the northernmost region (about 5 in 100,000) and in the southernmost regions (about 3 in 100,000). The lowest frequency, 1.3 in 100,000, is found in the central part of Sweden (with the capital, Stockholm).

Calculations are made of the gene frequencies and heterozygote frequencies according to the HARDY—WEINBERG law. In the northernmost region, these frequencies are estimated to be about twice those in the central region, intermediate values being noted for the other regions. Variations in the different counties about the average values in the respective regions are shown in Table 25.

An attempt is also made to calculate the heterozygote frequency, gene frequency and homozygote frequency on the basis of the marriages contracted between 1891 and 1936, according to their geographic distribution. It was necessary for this purpose to make some approximations of data obtained from the Swedish official statistics. With due reservation for these approximations, it is interesting to note the fairly good agreement between these »indirectly» estimated frequencies and those given above (*cf.* Table 25).

(24) A brief account is given of the extensive genealogic investigations, in which more than 8,000 ancestors in the 105 families of the present material were followed and traced. It was then found that no less than 29 of these families belong to 5 large family complexes (Figs. 5—9). Four of the family complexes are found in the northern half of Sweden, where they are largely continuous with respect to the regions in which the ancestors are distributed (Fig. 2). An especially interesting feature is that, in the past, a concentration of the birthplaces of the ancestors of the family complexes is found, not in small. remote regions of a markedly »isolate» nature, but in fairly central

regions of the respective counties, which do not have poor communications with other parts of the population. Obviously, it must be borne in mind that the population of northern Sweden has been sparser and more settled than that of southern Sweden.

(25) »Over-all» values of the heterozygote frequency in the whole country and its different parts, calculated according to the HARDY—WEINBERG law, are given under points 21 and 23. The condition for such a calculation is a panmictic population in genetic equilibrium. This probably does not apply to human populations. If the population of Sweden were divided into smaller, partial populations fairly isolated from each other, the calculated »over-all» values could be regarded as maximum estimates of the »true» average values. According to some authors, the latter amount to only a small fraction of the calculated »over-all» value.

The assumption is made that heterozygotes occur only within the partial populations of the parishes of birth of the affected persons, and not outside them. This assumption is obviously incorrect, but is made in order that a probable range of the »true» average heterozygote values may be calculated. The number of heterozygotes calculated under this assumption, related to the whole population, can then be regarded as minimum estimates of the »true» average values. They may, in any event, with some reservation be accepted as such, and are presumably the best estimates obtainable.

As in point 23, caution must be observed in evaluating the values for the individual counties, in view of the small size of the material. For the five large regions listed from north to south, the ranges estimated in this way for the heterozygote frequencies expressed in per cent are as follows: 0.5—1.4, 0.3—0.7, 0.5—1.0, 0.4—1.1, 0.5—1.1, and for the whole country 0.4—1.0 (columns (4) and (5), Table 26).

In the right-hand columns of Table 26 are given, as proportions of the population of the whole counties, the size of the partial populations in the birth parishes of (a) the affected persons alive in 1945, aged 10—49 years, (b) all the affected in the present material, (c) the 210 parents in the 105 families of the material. It may be justified to doubt such an assumption as that the heterozygotes exist only as a small fraction of the earlier calculated »over-all» frequency for the whole country.

The »isolate» effect is discussed. Reasons are given for avoiding too rigid an application of the »isolate» concept. The hypothesis that human populations, especially in a country like Sweden, have earlier been

divided into partial populations with fairly strict barriers is discussed. The urgent need is stressed of empirical investigations to determine the degree of accuracy of this hypothesis. Figures are given from the present material, in which the degree of inbreeding is strikingly high for our days. They seem to express a surprisingly lively population movement in the past, with marriages outside the »isolate» barriers. Owing to the special nature of the material these figures must, however, be interpreted with due caution.

(26) Calculations of the mortality show it to be increased in the affected female pupils at Tomteboda Institute, as compared to the general population. The small size of the sample does not, however, permit any conclusions. The mortality in the affected male pupils and in the unaffected sibs seems to correspond to that in the general population. Tuberculosis was responsible for the majority of deaths in the affected persons.

The marriage frequency is found to be significantly decreased in the affected persons of both sexes, being 47 per cent of the expected value in the males and 29 per cent in the females. An approximate calculation was made of the relative fertility of the homozygotes. With due reservations for all the sources of error, a mutation rate of the recessive gene, $m=2.3\cdot10^{-5}$, has been calculated, and is probably a minimum figure.

(27) The frequency of oligophrenia, psychoses, epilepsy and other disorders in the affected persons and their relatives is not found to differ significantly from the conditions in the general population. It can be stressed in particular that no genetically determined combination with deaf-mutism is present.

(28) It is evident that all the data collected and analyzed are in good agreement with the hypothesis that the condition in question is a hereditary, monohybrid recessive autosomal one with complete manifestation of the gene in double dose. This complete penetrance is valid with respect to the impairment of retinal function.

The degree to which the retinal function is impaired, is variable. This may be due to some extent to environmental, non-genetic factors. It is, however, most reasonable to assume that at any rate the greater part of this variability is determined by genetic modifiers.

Besides the existence of genetic modifiers of the main gene, it is not unreasonable to assume that the latter may occur in at least two alleles. It could then be presumed that the allele which results in the mildest im-

pairment of the retinal elements is less frequent in the population than the allele causing the severest impairment.

Genetic modifiers seem to be the most rational explanation of the incomplete manifestation of the main gene in its action on the tissues forming the lens and cornea. It is difficult to surmise whether the effect on the choroids is of a genetic nature or is purely secondary to the retinal damage.

Conclusions

The present study is based on a series of 175 cases of a hitherto unreported, hereditary form of congenital blindness or severe impairment of sight. This material was obtained through the records of the organization for the care and education of the blind in Sweden. Since the education of blind children has been enforced by law since 1897, it can be regarded as fairly complete.

It seems justified to put forward the hypothesis of a uniform condition, with a monohybrid, recessive autosomal mode of inheritance and complete manifestation. This hypothesis should, in any event, be valid for the great majority of cases comprising the present material.

It was not until combined genealogic and genetic-statistical studies had been made, and clinical data collected over a long period, that the clinical development and affinity of these apparently heterogeneous cases could be established with some degree of probability.

A constant feature is the defective vision, presumably congenital, consisting either of total amaurosis or of greatly impaired sight with loss of central vision. As a rule, there is a gradual deterioration in any remaining vision. No so-called tube vision was observed.

Electroretinographic studies have shown that the primary functional decrease is to be sought in the retinal elements. In their youth, most of the patients exhibited sparse, uncharacteristic retinal pigmentations, chiefly peripheral, which were generally diagnosed as retinochoroiditis, degeneration of the retina, or tapetoretinal degeneration. These changes are found to progress slowly with age. It is not until after 50 years of age that widespread atrophy, disclosing white areas of the sclera, is apparent.

Despite severe functional impairment, even to total amaurosis, visible fundus changes are lacking during the early years in a minority of cases. They sometimes appear later and progress, but may be absent at a fairly advanced age in some cases.

Cataract and keratoconus are common features, and show a distinct increase in frequency with age, as well as definite progression in the

individual case. The presence of keratoconus, which is otherwise so uncommon, is obviously of great value for a differential diagnosis.

It is evident that the pathologic gene acts on tissues forming both the retina and the lens and cornea. It is more difficult to surmise whether the choroid atrophy present in the older patients is a secondary phenomenon, or whether it is genetically determined.

It is assumed that the variability of the symptoms and the time development in the individual case are determined by genetic modifiers. It also seems reasonable to assume that more than one allele of the gene in question can occur in the population.

The disease is not combined with any psychiatric or neurologic disorder. It can be stressed in particular that no increased frequency of deaf-mutism is found, neither in the affected persons nor in their relatives. No classic case of retinitis pigmentosa has been recorded in the affected persons.

The disease in question is responsible for about 10 per cent of the cases of blindness in Sweden that reach school age. Its frequency in the general population can be estimated at about 3 in 100,000 and the gene frequency at 5 or 6 in 1,000. The heterozygote frequency in the population, an »over-all» value for the whole country, is estimated to be between one-half and one per cent. The disease seems to be spread over the whole country, but with a varying frequency.

The name *heredo-retinopathia congenitalis, monohybrida recessiva autosomalis* is suggested for the disease in question, unless a better term can be proposed which mentions other involved tissues as well.

The object of the present investigation was to make known the existence of this probable pathologic entity. Obviously, most of the work needed for its final elucidation remains to be done: histopathologic, electrophysiologic, biochemical and serological investigations, to mention only the most urgent of them.

APPENDIX

APPENDIX 1. *Marriages of various durations distributed proportionally according to the family size. Childless marriages excluded. General population of Sweden, Census 1930, Statistical Yearbook 1947, Table 25, p. 29. Expected and observed distribution of marriages of parents of affected.*

Duration of marriage in years	Number of children in family											Σ
	1	2	3	4	5	6	7	8	9	10	≥11	
5—10	0.3049	0.3239	0.1978	0.1030	0.0447	0.0168	0.0055	0.0018	0.0008	0.0004	0.0004	1.0000
10—15	0.1763	0.2515	0.2096	0.1465	0.0936	0.0590	0.0346	0.0169	0.0074	0.0028	0.0018	1.0000
15—20	0.1188	0.1849	0.1877	0.1537	0.1129	0.0844	0.0618	0.0432	0.0268	0.0143	0.0115	1.0000
20—25	0.0900	0.1534	0.1724	0.1512	0.1225	0.0963	0.0719	0.0536	0.0364	0.0246	0.0277	1.0000
25—30	0.0751	0.1372	0.1602	0.1496	0.1266	0.0998	0.0780	0.0604	0.0443	0.0312	0.0376	1.0000
≥30	0.0654	0.1090	0.1277	0.1284	0.1217	0.1092	0.0957	0.0804	0.0625	0.0441	0.0559	1.0000
	Expected distribution of families of different sizes in the 100 observed marriages between parents of affected											Number of marriages
5—10	0.9147	0.9717	0.5934	0.3090	0.1341	0.0504	0.0165	0.0054	0.0024	0.0012	0.0012	3
10—15	2.9971	4.2755	3.5632	2.4905	1.5912	1.0030	0.5882	0.2873	0.1258	0.0476	0.0306	17
15—20	1.4256	2.2188	2.2524	1.8444	1.3548	1.0128	0.7416	0.5184	0.3216	0.1716	0.1380	12
20—25	1.3500	2.3010	2.5860	2.2680	1.8375	1.4445	1.0785	0.8040	0.5640	0.3690	0.4155	15
25—30	0.9012	1.6464	1.9224	1.7952	1.5192	1.1976	0.9360	0.7248	0.5316	0.3744	0.4512	12
≥30	2.6814	4.4690	5.2357	5.2644	4.9897	4.4772	3.9237	3.2964	2.5625	1.8081	2.2919	41
Total expected	10.3	15.9	16.2	14.0	11.4	9.2	7.3	5.6	4.1	2.8	3.3	100
Total observed	7	18	17	9	14	5	10	7	3	6	4	100

APPENDIX 2. *Number born alive, and number surviving one year of age, general population of Sweden and affected individuals, 1891—1938. Statistical Yearbook 1947, Table 47, p. 63, and Table 48, p. 64.*

Birth period	No. born alive		No. per 1000 live-births surviving 1 year		No. surviving 1 year 1891—1938			Affected individuals born 1891—1938		
	Males	Females	Males	Females	Males	Females	Both sexes	Males	Females	Both sexes
	1	2	3	4	5	6	7	8	9	10
1891—1900	688,000	650,730	889.3	908.0	611,838	590,863	1,202,701	18	14	32
1901—1910	703,950	664,460	907.4	924.0	638,764	613,961	1,252,725	13	19	32
1911—1920	649,590	613,350	923.3	938.5	599,766	575,629	1,175,395	15	25	40
1921—1930	543,700	514,700	934.1	948.6	507,870	488,244	996,114	15	14	29
1931—1938	368,561	348,158	946.8	959.5	348,954	334,058	683,012	11	13	24
					2,707,192	2,602,755	5,309,947	72	85	157

APPENDIX 3. *Number of children in general population of Sweden born 1918—1937 who reached school age. Number registered as blind or with defective vision.* (SJÖGREN *and* LARSSON *1949 p. 22 and 23.) Number of affected who reached school age in the present material and born during the same period.*

Year of birth	No. of children alive at end of the calendar year in which they reached the age of 7			No. of blind children who reached school age according to records of Inspector and L			Number of affected in the present material who reached school age		
	Males	Females	Both sexes	Males	Females	Both sexes	Males	Females	Both sexes
1918—1927	531,543	511,262	1,042,805	163	164	327	13	14	27
1928—1937	429,420	413,537	842.957	158	95	253	14	17	31
Σ	960,963	924,799	1.885,762	321	259	580	27	31	58

APPENDIX 4. *Estimation of the frequency of the hypothetical heterozygote × heterozygote matings 1891—1936, by county.*

For standardization in view of the heterozygote × heterozygote matings with at least one child but no affected child, each marriage in the present material has been weighted according to its number of offspring, using the principles given on page 66. In those cases in which the partners were born in different counties, half the weight for this mating has been assigned to each of the two counties. Thus, the weighted figure 145 in column (5) of Table 21 has been distributed by county, the distribution being given in column (2) of Appendix 4.

Data are not given in the official statistics regarding the geographic distribution by county of the marriages in the general population contracted in 1891—1936 (see Table 21). The hypothetic assumption is made that they are distributed in approximately the same proportions as in the investigated sample of co-habiting married men (=existing number of marriages) at the 1945 census (see Statistical Abstract of Sweden, Population Census 1945 VII: 2, »one-twelfth sample» investigated parts of family statistics, Table A, p. 4). Correction is made for the number of childless marriages (see Table 2, pp. 4—5 in the same publication), *i. e.,* 35.4 per cent for the City of Stockholm and 20.5 per cent for the rest of the country. The percentage distribution by county of the marriages in the »one-twelfth sample» with at least one child is given in column (3). With the help of these figures, the marriages in the general population contracted in 1891—1936 and with at least one child are distributed by county. The figures in column (2) are then divided by the figures thus obtained. This gives the estimations of the frequency by county of heterozygote×heterozygote matings with at least one child recorded in column (4).

Using the figures in this column (4), the figures recorded in columns (2), (4) and (6) of Table 25 on page 76 have been calculated. In view of the many approximations and hypothetical assumptions, these figures should be used only with the greatest caution.

(1)	(2)	(3)	(4)
County	Weighted no. of marriages 1891—1936 in the present material	Percentage distribution by county of existing marriages with at least one child; 1 : 12 sample, 1945 Census	Estimated frequency heterozygote × heterozygote matings
Norrbotten	8.1	3.25	0.000,171
Västerbotten	8.0	3.26	0.000,167
Västernorrland	8.2	4.32	0.000,130
Jämtland	4.7	2.04	0.000,159
Gävleborg	10.2	4.35	0.000,161
Kopparberg	3.6	3.99	0.000,062
Västmanland	0.8	3.04	0.000,019
Uppsala	1.8	2.30	0.000,054
Stockholm county	2.6	5.36	0.000,034

(1)	(2)	(3)	(4)
Stockholm city	2.0	8.56	0.000,016
Örebro	2.3	3.87	0.000,041
Södermanland	1.8	3.37	0.000,038
Värmland	6.3	4.01	0.000,108
Göteborg and Bohus	8.4	7.99	0.000,072
Skaraborg	5.9	3.48	0.000,116
Älvsborg	9.8	4.89	0.000,137
Halland	3.0	2.12	0.000,097
Östergötland	10.1	5.34	0.000,129
Jönköping	3.8	3.79	0.000,069
Kalmar	11.4	3.52	0.000,221
Kronoberg	4.5	2.19	0.000,141
Blekinge	2.1	2.09	0.000,071
Gotland	2.8	0.85	0.000,225
Kristianstad	10.9	3.55	0.000,211
Malmöhus	11.9	8.44	0.000,097
Total	145.0	100.0	

APPENDIX 5. *Oligophrenia, psychosis, epilepsy and some other diseases in the 175 affected individuals, their 303 unaffected sibs, and 210 parents.*

1. *The Affected Individuals*

F. 7 a. ♂ 47 years old. Schizophrenia at 39 years of age, subsequently chronically ill.

F. 9 a. ♀ d. 33 years old of »polyserositis». Earlier mentally healthy. Epileptic seizures started at 8 years of age; referred to Lund for special-class instruction. Seizures increased in frequency; coincident progressive mental change of organic type. Epilepsy and organic dementia since 8—9 years of age. — Sister, F. 9 b, good intelligence, has permanent post as typist at magistrates' court.

F. 12 b. ♂ 32 years old. Severe oligophrenia deaf-mute and paretic; epileptic seizures, »large, rachitic head». In asylum since 5 years of age. — Sister, F. 12 a, intellectually somewhat below average. Otherwise N. A. D.

F. 22 a. ♂ d. 17 years old of pulmonary tbc. Epidemic encephalitis at 1 year of age, subsequently deaf-mute. Attended school for deaf and dumb. Like brothers, high intellectual level, despite his triple handicap of blindness and deaf-mutism.

F. 23 a. ♀ 54 years old. Impaired hearing since age of 44 years, earlier N. A. D. Works as trained medical gymnast.

F. 25 a. ♂ 18 years old. Diabetes since 8 years of age; insulin therapy. Since 11 years old, occasional epileptic seizures, usually in connexion with insulin adjustment. Diabetes and epilepsy. — Sister, F. 25 a, mentally and physically healthy. Intelligence of both corresponds to average.

F. 35 a. ♀ 9 years old. In last year at Tomteboda primary school. Mentally dull (to be referred for special-class instruction).

F. 41 b. ♂ 54 years old. At 54 years of age, manic depressive psychosis; recovered.

F. 43 b. ♀ 44 years old. After 3 years at TI, referred to Lund for special-class instruction, as »poor intelligence». »Mentally dull.» — Sister, F. 43 a, good intelligence, above average.

F. 48 a. ♂ d. 43 years old of carcinoma of the stomach. At 25 years of age, schizophrenic psychosis, recovered after some months. At 27, next psychotic bout, did not recover. Schizophrenia.

F. 49 a. ♂ 34 years old. From 15 to 24 years of age, occasional grand mal seizures. Good intelligence, above class median. Gifted technically. Epilepsy cured. Mentally healthy.

F. 62 a. ♂ d. 3 ½ years old of acute glomerulonephritis. »Blind since birth.» Unable to walk or talk. Severe oligophrenia. — Sister, F. 62 b, mentally healthy.

F. 65 a. ♂ d. 24 years old, cause of death not stated. At 7 month of age, ophthalmologist consulted: »incurable retinal disease». Severe oligophrenia with endocrine dysfunction, epileptic seizures since 13 years of age. — Blind sister, F. 65 b, good intelligence. Married; 2 healthy children.

F. 76 c. ♀ 45 years old. Admitted to Tomteboda primary school on diagnosis retinochoroiditis of both eyes. After 2 years referred as mentally deficient to special-class schooling in Lund. — 2 blind brothers: F. 76 a and F. 76 b, both mentally healthy, intelligence above class median.

F. 81 b. ♂ 45 years old. Epileptic seizures since 14 years of age. Progressive organic-neurologic dementia evident since age of 7. At 11 years of age sent to TI; unsuccessful, transferred to asylum in Lund. — 2 blind sibs, F. 81 a and b, mentally healthy, good intelligence.

F. 83 a. ♀ 28 years old. Since 16 years of age, 1—2 epileptic seizures a month, usually during menstruation. Controlled by medication. Neuropsychiatric status otherwise N. A. D. Intellect corresponding to average. Epilepsy.

F. 86 b. ♂ 11 years old. At 2 years of age admitted to children's home at Tomteboda and then to primary school. Owing to imbecility (I. Q. 47) transferred to Lund for special-class instruction. — Brother, F. 86 a, good intelligence; lower certificate examination after TI.

F. 90 a. ♀ d. 4 ½ years old of »stroke». Severe oligophrenia. Stated to be able to talk, but unable to walk or feed herself. »Blind since birth». — Brother, F. 90 b, mentally normal, has own brush-factory.

F. 95 a. ♀ 26 years old. Severe oligophrenia. — Brother, F. 95 b, intelligence above the median of the class, 16.5 marks against 12.9.

F. 97 a. ♀ d. 25 years old of chronic glomerulonephritis. Schizophrenia since 18 years of age.

F. 102 c. ♀ 31 years old. First 4 years at school N. A. D. Since 11 years of age, catatonic phases and progressive schizophrenia.

2. *The Unaffected Sibs* (*not impaired vision*)

F. 15. ♂ 68 years old. Chronic schizophrenia. Age at onset not definitely stated.

F. 54. ♀ d. 12 years old of paradysentery. Severe oligophrenia. Vision N. A. D. Had 3 affected sibs, all mentally healthy.

F. 83. ♀ 22 years old. Severe oligophrenia. — One sister, F. 83 a, mentally healthy, but epilepsy since 16 years of age.

F. 85. ♂ d. 10 years old; cause of death unknown. Organic post-meningo-encephalitic dementia.

F. 90. ♂ 31 years old. Intellectually below average. Imbecillitas.

F. 94. ♀ 45 years old. Married, 2 children. Earlier healthy, since 39 years of age progressive paraphrenia. Schizophrenia.

3. *The Parents*

F. 17. ♂ d. 37 years old of pulmonary tbc. »Born deaf-mute.» ♀ 72 years old. »Deaf and dumb after illness in early childhood.» Both mentally healthy; vision N. A. D. — Daughter, F. 17 a, hearing N. A. D., mentally healthy.

F. 24. ♀ 46 years old. Dullness.

F. 34. ♂ 48 years old. Retinochoroiditis. Blind from birth. Secondary case, brother of F. 33 d.

F. 61. ♀ d. 43 years old. Mental disease since 33 years of age. Chronic schizophrenia.

F. 83. ♀ 51 years old. Schizophrenia since 39 years of age.

F. 84. ♀ d. 57 years old of bronchopneumonia. — Cerebral arteriosclerosis with mental symptoms.

F. 87. ♂ 61 years old. Since childhood, small, central circumscribed corneal opacity in right eye. Vision N. A. D.

F. 92. ♂ 38 years old. For past few years, impaired hearing.

APPENDIX 6. *Summary of the case records.*

An extract from the case records and a chronological survey of the data in the individual cases are given in Table 3. At the head of this table are given the meaning of the various symbols used, as well as the name of the investigators or clinics and institutions, where the investigations were performed on the relevant occasions. It is suitable when reading Table 3 to compare it with the records in this Appendix. A diagnosis and ophthalmologic status for patients who have been pupils at Tomteboda Institute not followed by the initials of an investigator denotes that the examination was made by the ophthalmologist in charge at the Institute. These are denoted by T in Table 3. In other cases, the initials of the examiner are given (*cf.* Table 3).

F. 1 a (R) Tl. ♂ b. 1900

Retinochoroiditis. *1909*: Vision: R. E. and L. E.=1/60. — *1955*: Vision: R. E. and L. E.=0. Bilateral, dense diffuse cataract. Pupils did not react to light. Irregular, slow, undulating eye movements; unable to control direction of eyes. Before and during school age, sufficient sight to permit skiing. Could distinguish objects, and at very close range recognize persons by contours; could never distinguish features. At school, able to do paper cut-outs at very close range. Noticed that he had »a few spots» at the sides with which he had better vision. Could only locate them with difficulty, and by twisting and turning his head. Had not had tube vision. Attended local school for one year, then sent to Tomteboda. Gradual deterioration in sight. Stated that in about 1945 he could still perceive light from lamps etc., but this ability subsequently lost. (O—n). — *1956*: Admitted to Eye Clinic, Karolinska Sjukhuset. Diagnosis: Inveterate, bilateral retinochoroiditis and bilateral, complicated cataract. On admission, vision: R. E. and L. E.=0. Divergent strabismus, nystagmus-like eye movements; dense, bilateral cataract, preventing inspection. *ERG* of both eyes extinguished. — Left eye: intracapsular extraction of lens and peripheral iridectomy. Postoperative course uneventful. On discharge, uncertain perception of light in left eye, no localization. In fundus of left eye, advanced changes, consisting of large, white foci and scattered pigmented spots over whole fundus (Eye Clinic, Karolinska Sjukhuset).

F. 1 b (R) Kr. ♂ b. 1905

Defective sight since birth. Difficulty in keeping up at school. Exempted from conscription on account of poor sight. Attended Vocational Training School for Blind Men in Kristinehamn. — *1946*: Vision: R. E.=Finger counting 1 m; L. E.=Bare perception of light. Discs apparently normal, no distinct changes. Over whole fundi, scattered, small round pigmentations and larger irregular ones, as well as several larger greyish spots (foci). Pupils reacted slightly to light. No actual nystagmus, but irregular eye movements. (A—m). — *1949*: In September, thrombosis of sinus cavernous with acute onset; pain in left eye, swelling and protrusion of disc. — *1951*: In right retina, numerous small exudates, contrasting to spotty, greyish-yellow colour of retina. Left retina similar to right, with numerous, greyish-yellow exudates scattered over more or less atrophied retina. Discs somewhat atrophied, not sharply

delimited. Vessels narrow. »Probably retinitis pigmentosa on hereditary basis» (P—å Hospital).

F. 1 c (R). ♀ *b. 1909, d. 1951 of carcinoma of the vulva with metastases*

According to sibs, defective sight since birth like other blind sibs, but nevertheless managed best of them. Like brother, born in 1905, struggled through local elementary school. There seems to have been some progression, as in sibs, but the initial condition was poor. — *1942*: Had ayways had poor sight, but was able to attend ordinary school; could see to read with difficulty. Unable to see in dark. Sight now worse; unable to read for past few years. Vision: R. E. = 1/60; L. E. = 0.5/60. No improvement with glasses. Remains of temporal vision peripherally on both sides. Some posterior polar cataract. Extensive fundus changes, somewhat atypical, and with greyish-yellow spottiness as well. Arteries narrow; peripherally, partly obliterated. Discs somewhat sallow. Diagnosis: retinitis pigmentosa. (G—m, Södersjukhuset).

F. 2 a (R) Ups. ♀ *b. 1890*

School for Blind in Uppsala. Said to have had poorest sight of sibs since birth. — *1946*: Vision: R. E. and L. E. = 0. Bilateral cataract. Bilateral keratoconus. Corneal opacity in lower lateral quadrant of left eye. (A—m). — Married to man blind since 3 years of age; 9 healthy children aged 17—32 years, one of them in Air Force.

F. 2 b (R) TI. ♂ *b. 1895*

Retinochoroiditis. *1908*: Vision: R. E. = 1.5/60; L. E. = 1.5/60; *1914*: do. — *1946*: Vision: R. E. and L. E. = Perception of light. Bilateral cataract. (A—m). — Operated on for cataract, but after-cataract developed. Owing to complicating haermorrhages, the fundi could never be inspected. The patient nevertheless received the diagnosis retinitis pigmentosa since »two sibs have retinitis pigmentosa, the patient has always had poor vision and difficulty in seeing at night». (B—n Hospital, 1952).

F. 3 a (R) TI. ♂ *b. 1889*

Retinochoroiditis. *1901*: Vision: R. E. = 1/60; L. E. = 1.5/60. Able to read the time and large headlines in papers. — *1946*: Vision: R. E. and L. E. = Perception of light. In fundi, alternating large, slate-coloured areas and both large and small pigmented spots, not resembling bone corpuscles, over whole fundi. Discs blurred. Slow, undulating eye movements. (A—m).

F. 3 b (R). ♂ *b. 1891, d. 1895*

»From the start, sight worse than that of 3 a.»

F. 3 c (R). ♂ *b. 1893, d. 1897*

»Completely blind since birth.»

F. 3 d (R). ♂ *b. 1894, d. 1900*

»Poor sight since birth.»

F. 3 e (R). ♂ b. 1908, d. 1911

»Defective sight since birth. — All sibs thus died before starting school.»

F. 4 a (R) TI. ♀ b. 1933

Retinochoroiditis. Vision: R. E.+9=3/50; L. E.+9=2/50. *1946*: Fundus of R. E.: disc very blurred, vessels normal. In the macula, the retina was atrophic in a disc-sized area of oval shape. In its margin, several small black pigmented spots. Fundus of L. E.: disc very blurred. In the macula, the retina was irregularly atrophic, with a few small pigmented spots and one somewhat larger, triangular spot. None in the fovea. In the periphery, small round black pigmented spots, some of them more elongated and irregular. (O—n). — *1953*: Status quo. (O—n).

F. 5 a (R) TI. ♀ b. 1891, d. 1907 of pulmonary tuberculosis

Bilateral optic nerve atrohpy (*1902*) and bilateral incipient cataract (*1907*). Vision: R. E. and L. E.=1.5/60. — The patient was not traced primarily, but through relationship with the R-complex.

F. 6 a (R) TI. ♀ b. 1910

Retinochoroiditis. *1925*: Vision: R. E.=Hand movements; L. E.=0.2/60. Discs seemed poorly delimited. Numerous foci of pigment over whole fundus. (According to District health officer, in same year, »the appearance of the fundi resembles choroiditis disseminata».) — *1956:* Sight poor since birth, still worse after 35 years of age. Vision: R. E. and L. E. = Perception of light. Nystagmus. Both corneas N. A. D. Fairly large, central round cataract in anterior cortex of both lenses. Fundi: discs somewhat pale, vessels very narrow. The fundi were strewn with largely confluent, black pigmented spots, irregularly shaped, round and angular. Pigmented spots were also present in both macular regions; round, fairly small, not as closely spaced as in rest of fundi. The general colour, apart from the pigmented spots, was the usual red, possibly somewhat yellowish-red. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 7 a TI. ♂ b. 1899

Bilateral congenital amblyopia. *1908*: Vision: R. E. and L. E.=4/60. Completely colour blind. Photophobia. — *1946:* Vision: R. E. and L. E=Finger counting $<$ 1 m. Stated twilight vision to be best. Extremely photophobic; screwed up his eyes, difficult to examine. Fundi apparently normal. (A—m).

F. 7 b TI. ♀ b. 1901

Bilateral congenital amblyopia. *1908*: Vision: R. E. and L. E.=5/60. Completely colour blind. No photophobia. — *1947—48*: Bilateral keratoconus and corneal opacities. Mature cataract in right eye, incipient in left. — Operation on right eye (P—å Hospital). — *1955*: After-cataract; fundi could therefore not be seen clearly, but »as far as could be seen, no degenerative changes, but highly uncertain». Was extremely photophobic and difficult to examine. Vision: L. E.: finger counting at $1\,^1/_2$ m. (P—å Hospital).

F. 7 c ♀ *b. 1909, d. 1912 of meningitis*

Defective sight since birth.

F. 7 d Tl. ♂ *b. 1912*

Bilateral congenital amblyopia. *1920*: Vision: R. E. = 1/60; L. E. = 2/60. Pupils reacted sluggishly; photophobia. No evident fundus changes, possibly slightly coarser pigmentation than normal. — *1946*: Intense photophobia. Vision: finger counting at < 1 m. Nothing definitely pathologic could be seen in the fundi, but the patient constantly screwed up his eyes, and was extremely difficult to examine. (A—m). — *1956*: Had always had poor sight. No change noticed with years. Extreme photophobia. Vision: R. E. = Finger counting at 1 m (barely); L. E. = Finger counting at $^1/_2$ m. Inappreciable, irregular eye movements. Pupils reacted normally. Both corneas normal. Lens: paracentrally, temporally in posterior cortex a round, irregularly dense cataract in right lens. Left lens clear. Fundi: normal colour. No pigmentary changes either centrally or peripherally. Discs somewhat pale, vessels somewhat narrow. (O—n). *1956*: *ERG* extinguished.

F. 8 a (*S*) *Tl.* ♀ *b. 1920, d. 1934 of pulmonary tuberculosis*

Retinochoroiditis. *1928*: Vision: R. E. = Perception of light; L. E. = Hand movements. Pupils reacted to light. Large, slightly choratrophic focus centrally.

F. 8 b (*S*) *Tl.* ♂ *b. 1921*

Retinochoroiditis. *1928*: Vision: R. E. = Perception of light; L. E. = Hand movements. Pupils reacted to light. Both centrally and peripherally, choratrophic foci with sparse pigment. — *1946*: White atrophic focus (more centrally?), as well as small, black pigmented spots more peripherally. Vision: R. E. and L. E. = Bare perception of light. (A—m).

F. 8 c (*S*) *Tl.* ♂ *b. 1934*

Central degeneration of retina. *1942*: Pupils reacted to light; lively nystagmus. Discs normal. Vision: R. E. and L. E. = 1/60. In macula, a reddish, oval focus with scanty pigmentation in the centre. — *1946*: Discs somewhat pale, arteries narrow; in a disc-sized area in the macula, depigmentation to pale red colour and pigment aggregated into a black, reticular formation. Vision: R. E. = 4/50; L. E. = 2/50. (O—n).

F. 9 a (*S*) *Tf.* ♀ *b. 1909, d. 1942 of polyserositis*

No objective changes. *1916*: Vision: R. E. and L. E. = Perception of light. Discs normal colour, vessels of ordinary calibre. No evident fundus changes in other respects. Marked nystagmus. Eyes deep-set. — Epileptic seizures started; transferred to Lund after two years; difficulty in following instruction. In Lund, slowly progressive organic-neurologic dementia. Ophthalmologic diagnosis there: retinochoroiditis. — *1925*: Bilateral, central corneal opacities and keratectasia. Vision: R. E. and L. E. = 0. Fundi could not be seen. (Lund).

F. 9 b (S) TI. ♀ b. 1929

Retinochoroiditis. *1936*: Vision: R. E.=Perception of light; L. E.=0. Inappreciable opacity temporally in both lenses. Retinitic atrophy of discs. Very numerous small grains of pigment and a few larger, round pigmented foci peripherally. — *1945* TI: Degeneration of the retina. Vision: R. E.=Perception of light; L. E.=0. — *1946*: Pupils did not react to light. Vision: R. E. and L. E.=0. A few scattered large pigmented spots, and several smaller round ones peripherally. (A—m). — *1956*: Poor sight since birth. Able to distinguish between light and darkness when difference very marked. Had not noticed any change in vision. Some irregular eye movements. No definite perception of light was noted. Bilateral keratoconus. Scar centrally in left cornea (had »inflammation of cornea» in 1948). Fine spoke-formed cataracts in both lenses. Fundi: discs somewhat pale, vessels narrow. Numerous, small greyish-white spots in fundi, but only a few small and medium-sized clumps of pigment and some branched ones; mainly present half-way peripherally. No definite alterations in central parts. (O—n). — *1956*: *ERG* of both eyes extinguished. — After schooling at Tomteboda, attended Folk High School and did secretarial training. Employed as typist in communal civil service department. Intelligence over average; total marks 16 as compared to class median 12.8.

F. 10 a (S) TI. ♀ b. 1939

Congenital amblyopia. *1947*: Vision: R. E. and L. E.=0. Both medias normal. Discs somewhat pale. Maculas N. A. D. At some distance from the centre of the fundi as well as more peripherally, the pigment was clumped into small dots and a few larger ones. In between, the fundus was yellowish-red. Pupils did not react to light. Suggested keratoconus. — *1953*: Vessels narrow, otherwise status quo. — *1955*: *ERG* of both eyes extinguished. — *1956*: Irregular eye movements. Medias and corneas clear. Suggested keratoconus. Fundi: discs somewhat pale with peripherally atrophy. Vessels somewhat narrow. Maculas normal. Peripherally, moderate number of small and medium-sized pigmented spots, both round and irregularly triangular. Colour of fundi yellowish-red in periphery. (O—n). *ERG* of both eyes extinguished. —

The following was a nephew of F. 10 a on the sister's side; he was later a pupil at Tomteboda and is therefore not included in the investigation.

F. (S) Tf. ♂ b. 1948

1955: Congenital amblyopia. Vision: R. E. and L. E.=0. Moderate nystagmus. Corneas clear. Suggested keratoconus. Lenses clear. Discs somewhat pale, arteries somewhat narrow. Periphery possibly somewhat pale and small-spotted. (O—n). — *ERG* could not be recorded on account of the boy's anxiety. Otherwise lively and intelligent.

F. 11 a (S) TI. ♂ b. 1907

Retinochoroiditis. *1918*: Vision: R. E.=Hand movements; L. E.=0.2/60. — *1956*: Had always had poor sight; no definite change with years. Occasional, rapid nystagmus, otherwise some irregular eye movements. Vision: R. E. and L. E.=Weak perception of light. Strong light required. Pupils reacted weakly

to light. Corneas clear. Cataract in posterior cortex of both eyes, central, round, same in both lenses. Fundi: numerous black pigmented spots, mainly irregular, large and partly confluent. Discs pale, vessels narrow. Maculas could not be definitely evaluated. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 11 b (*S*) *TI.* ♂ *b. 1910*

Retinochoroiditis. *1918*: Vision: R. E. = 1/60; L. E. = Perception of light. — *1956*: Sight had always been poor; possibly some exacerbation in youth. Earlier could often see lamps; no longer possible. Vision: R. E. = 0; L. E. = Faint perception of light. Right pupil did not react to light; left reacted weakly. Moderate, irregular eye movements. On right cornea, a scar after injury by stone in youth. Marked keratoconus. Right eye: dense cataract, fundus not visible. Left eye: moderately dense cataract, fundus not visible. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 12 a (*S*) *TI.* ♀ *b. 1913*

Retinochoroiditis. *1920*: Vision: R. E. = 0; L. E. = 0. — *1946*: Could not distinguish between light and darkness, but irritated by strong light directly in eyes. A few round and irregular »dabs» of pigment, chiefly peripherally over the fundi. Moderate keratoconus. (A—m). — Total marks 9.5 as compared to class median 11.5.

F. 12 b (*S*) *L.* ♂ *b. 1914*

»Severe idiocy, deaf-mute, paretic, epileptic seizures.» Sent to Asylum in L—d. — Cataract in right eye and left-sided optic nerve atrophy (L—d). Blind in both eyes from birth. (L—d).

F. 13 a TI. ♂ *b. 1903*

Retinochoroiditis of right eye and adherent cataract of left eye. *1912*: Vision: R. E. = 2/60; L. E. = 0. — *1946*: Vision: R. E. = Finger counting at 1 m; L. E. = 0. Marked photophobia but unable to see at dusk. Irregular eye movements; screwed up his eyes. Black, irregularly shaped clumps of pigment could be glimpsed. The discs could not be discerned; patient difficult to examine. Extensive but transparent corneal opacity; left pupil filled by cataract. (A—m). — *1956*: L. E.: amaurosis and cataract; R. E.: inveterate choroiditis. Blind in left eye since birth. Inappreciable sight in right eye. Vision: R. E. = Finger counting at 1—1 ½ m; L. E. = amaurosis. Right eye: pale; no aqueous flare. A few corneal opacities. Left eye: pale, extensive corneal opacities, especially in lower part. Dense cataract; fundus could not be seen. Tension: soft. Right fundus: large atrophic foci with spots of pigment. (S—n, Eye clinic, Karolinska Sjukhuset). *ERG*: R. E. subnormal; L. E. extinguished. *Flicker ERG*: pathologic. (G. Karpe).

F. 14 a (*D*) *TI.* ♀ *b. 1926*

Congenital amblyopia. *1935*: Vision R.E. +4 = 2.5/50; L.E. +4 = 2/50. Media and fundus of both eyes normal. — *1936:* Suspected coarse pigment in periphery. — *1943:* Vision: R. E. and L. E. ± 0 = 0.1; visual field for hand movements

normal. No objective changes. — *1946*: Just able to get about alone; pupils reacted to light. Very sensitive to light, screwed up eyes constantly; difficult to examine. Nothing definitely pathologic observed in fundi. (A—m). — *1946*: Vision: R. E. and L. E. = 4/50, no improvement with glasses. Discs pale, otherwise normal. Difficult to examine. (U—å Hospital). — [Evident from records that the patient had from a very early age been extremely sensitive to light, and had poor daylight vision. Diagnosis 1928: »Retinitis pigmentosa and nyctalopia». (Provincial health officer)].

F. 15 a (D). ♂ b. 1880

Struggled through local elementary school, where teacher devoted special attention to him and his brother. Both had had poor vision since birth. Could distinguish outlines of people but not details. Managed out-of-doors and could even cycle in youth. Had always had poor vision, but believed that it had deteriorated in recent years. — *1956*: Could distinguish dark and light surfaces but not colours. Ordinary examination of colour sense impracticable. Vision: R. E. +4 (Finger counting at 1 ½ m) = 1—2/50; L. E. +4 (Finger counting at 2 m) = 2/50. Inappreciable irregular eye movements. Pupils reacted well to light. Medias clear. Fundi: in macular region of right fundus, but not centrally, a pale, round atrophic focus about 1/3 of a disc in size; no marked accumulation of pigment in its margin. Otherwise, both eye-grounds entirely normal, both centrally and in periphery, as were discs and vessels. (O—n). *1956*: *ERG* of both eyes normal. *Flicker ERG:* pathologic. (G. Karpe).

F. 15 b (D). ♂ b. 1882

Greatly impaired sight since birth. Could distinguish outlines but not details. At school, allowances were made for his poor sight. Able to get about out-of-doors with help of hearing. Managed somewhat better earlier, but on whole vision unchanged. Much bothered by sunlight. — *1946*: intense photophobia; difficult to examine. Finger counting at 2—3 m. No cataract or keratoconus. Fundi: no definite changes noticeable, but difficult to examine. (A—m). —

F. 16 a (D) TI. ♂ b. 1896

Congenital amblyopia. *1905:* Vision: R. E. and L. E. > 0.1. Nystagmus, night blindness, otherwise nothing objective. — *1910*: Vision: R. E. and L. E. +3 > 0.1 = Jaeger type 3 with difficulty; »Defective sight and trembling eyes since birth.» — *1946*: Just able to get about alone. Some »nystagmus» on attempt to fixate. Highly sensitive to strong light and sun. Nothing definitely pathologic observed and discs seemed to be normal. Able to read large type for short time with magnifying glass quite close to the eye. (A—m). — *1956*: Defective vision since birth, about the same since (somewhat poorer at close range, probably due to presbyopia). Twilight vision better than daylight vision. Vision: R. E. +4 (astigmatic corr. produced little improvement) = 0.1 (barely); L. E. +4 (astigmatic corr. produced little improvement) = 0.1. No noteworthy eye movements. Pupils reacted to light. Visual fields normal. Corneas and medias clear. (Javal R. E. 2 70°; L. E. 2 110°.) Fundi: discs and vessels normal. Peripherally in lower part of left fundus and centrally in both maculas, pale

atrophic areas with slight displacement of pigment; appearance as in senile degeneration of the macula. Nothing else noteworthy with respect to colour of fundus and pigment. (O—n). — *1956*: *ERG* of both eyes subnormal. *Flicker ERG*: pathologic. (G. Karpe).

F. 17 a (D) TI. ♀ b. 1906

Retinochoroiditis. *1913*: Vision: R. E. and L. E.=Hand movements. Retinitic atrophy of the discs. Finely divided pigment scattered over the albinotic eye. — *1955*: Vision: R. E. and L. E.=Perception of light. Visual fields could not be definitely evaluated, but no limitation seemed to exist. Pupils reacted to light. Media of both eyes clear. Fundi: discs somewhat blurred, only slightly pale; large atrophic foci around discs. Vessels somewhat narrow. Fundi yellowish-red. Numerous small, round pigmented spots, not resembling bone corpuscles, confluent in some places. Fewer pigmented spots in central parts of fundi than peripherally. (O—n). — *1955*: *ERG* of both eyes extinguished.

F. 18 a (A) TI. ♀ b. 1922

Retinochoroiditis. *1930*: Vision. R. E. and L. E.=0. Marked nystagmus. Fairly wide, reactionless pupils. Medias clear. Numerous, partly pigmented foci in macular regions. Atrophy of discs. — *1932*: In centre of fundus in macular region, a large choratrophic focus. Discs pale but no marked constriction of vessels. — *1946*:Vision: R. E. and L. E.=Perception of light—0. Marked nystagmus, making examination difficult. Pupils reacted weakly but definitely to light. In the right macular region, a large whitisch focus. Small black flecks of pigment in the periphery of both fundi. Discs sallow. (A—m). — *1956*: R. E. and L. E.=Faint perception of light. Pupils reacted to light, but the left only faintly. Rapid nystagmus. Cornea of both eyes clear. Iridodonesis. The lenses were poorly attached and were tremulous on eye movements. (In the autumn of 1955, the left lens was dislocated into the anterior chamber, with a secondary rise in tension. The lens reattached. Since then, the patient has used a miotic in both eyes.) In lens of both eyes a moderate posterior cataract of irregular shape, as well as a smaller, round cataract in anterior cortex. Fundi: discs somewhat pale, vessels narrow. Yellowish-white atrophy of right macula, but not of left. Scattered, pale atrophic foci of varying size in both fundi, and medium-sized, usually round pigmented spots in periphery. (O—n). — *ERG* not performed.

F. 19 a (A) TI. ♂ b. 1888, d. 1906 of pulmonary tuberculosis

1889: Bilateral retinochoroiditis; stated to have been »born blind», no other notation. — Evident from the sanatorium records that, apart from tuberculosis and blindness, there was nothing else pathologic. Mentally normal. Autopsy: situs inversus viscerarum.

F. 20 a (A) TI. ♀ b. 1877, d. 1898 in an accident

1890: Bilateral congenital amblyopia. One year later at Tomteboda, recorded as bilateral atrophy of discs. »Almost totally blind» (=perception of light).

F. 20 b (A) TI. ♂ b. 1879, d. 1903 of pulmonary tuberculosis

1890: Bilateral congenital amblyopia. One year later at Tomteboda, recorded as bilateral atrophy of discs. Almost totally blind. — The scanty records are practically identical for both sibs.

F. 21 a (A) TI. ♀ b. 1891, d. 1908 of pulmonary tuberculosis

Bilateral retinochoroiditis. *1903*: Vision: R. E.=1/60; L. E.=3/60. On both sides, numerous small pigmented foci over the whole fundus.

F. 22 a (A) Hä—Lu. ♂ b. 1914, d. 1931 of pulmonary tuberculosis

Meningitis at 1 year of age; hearing subsequently impaired and could not talk. Attended school for deaf-mutes and then Institute for Blind in Lund. Evident from the records that, despite his severe handicaps and deficient upbringing (in foster-home as a small child), his intelligence was on a high level. *1925* (Lund): Vision: R. E and L. E.=Finger counting at 2 m but with uncertainty. Sallow, somewhat blurred discs and retinal pigmentations. — [Most probable that blindness was on the same hereditary basis as that of brothers. Deafness, on the other hand, was presumably a sequel of meningitis. No other case of deaf-mutism recorded in the large family complex. (A—m)].

F. 22 b (A) Kr. ♂ b. 1917

Struggled through elementary school, then to Vocational Training School for the Blind in Kristinehamn. — *1935* (Provincial health officer): Vision: R. E.=1/60; L. E.=0.1. Stated that he had had good sight until 7 years old, when he started to see badly after blow on right temple. Stated that he saw well with the left eye, as well as earlier. Fundi: typical, sparse retinitis pigmentosa spots, chiefly in the periphery, a few close to it. Discs rose-coloured with somewhat indefinite margins. Arteries somewhat narrow. Otherwise nothing abnormal. Visual fields tested with hand movements showed some limitation, but the patient had difficulty in fixating. — *1946:* Vision: R. E. and L. E.>>Perception of light? Pupils reacted, although inappreciably, to light. No definite changes in discs. Over both fundi, scattered, sparse black angular pigmented spots and smaller rounded ones, increasing in number peripherally. (A—m).

F. 22 c (A) Kr. ♂ b. 1921

Struggled through elementary school, then to Vocational Training School for the Blind in Kristinehamn. — *1953* (Outpatient Eye Clinic, Serafimerlasarettet): Vision: R. E.=1.5/60; L. E.=3/60. No improvement with glasses. Medias clear. Fundi of both eyes, chiefly the right: slighly sallow disc with somewhat blurred margins. In periphery, pigment masses, not entirely typical of retinitis pigmentosa in appearance, increasing in number outwards. Great limitation of visual fields in both lateral directions. Diagnosis: »Most probably retinitis pigmentosa, despite not fully typical findings». — *1946*: Vision: R. E. and L. E.=Perception of light. Pupils reacted to light. No definite changes in discs. Sparse, scattered black pigmented spots of irregular shape and smaller rounded ones over the whole fundus, increasing in number peripherally. —

Matriculated (Studentexamen) in 1943 after 4 years' study. Studying languages at University of Stockholm. (A—m). — *1955:* Took Fil. Kand., studied psychology, employed as speech therapist. Intensely irritated by strong light and sunlight. Pigmentary changes in fundi appeared more extensive than in 1946. Keratoconus (not present in 1946) with no opacities in right eye, a few grey spots centrally in left cornea. Vision: R. E. and L. E.=Perception and localization of light temporally. Pupils reacted well to light. Visual fields difficult to evaluate, but the beam of light was definitely recognized in the temporal direction, best by the left eye, but not in other directions. Fundi: discs somewhat blurred and yellow but not pale, of usual size. Small area of peripapillary atrophy. Vessels somewhat narrow. Colour of fundi yellowish-red. In the centre, plentiful clumps of black pigment; nasally, a few small round grains of pigment, numerous such grains temporally. At this site (temporally) the fundus was more yellowish-grey in colour. (O—n). *1956*: *ERG* of both eyes extinguished.

F. 23 a (*A*) *TI.* ♀ *b. 1891*

Bilateral retinochoroiditis. *1904*: Vision: R. E.=0.1/60; L. E.=Perception of light. Slate-grey foci scattered over whole fundus. — *1946:* Vision: Bare perception of light. Incipient, bilateral keratoconus. Bilateral cataract, in left eye filling the whole disc. Fundi: left could not be seen; right partly visible, black pigmented spots of varying size scattered over whole visual field. — Mentally and neurologically normal. Has private practice as masseuse. Impaired hearing since 1935—36; hears high conversational tone at 4 m. (A—m).

F. 24 a (*A*) *TI.* ♂ *b. 1930.*

Congenital amblyopia. *1939:* Vision: R. E.+2.5=0.1; L. E.+2.5=4/50. Nystagmus. No objective fundus changes. — *1946*: Rapid nystagmus. Photophobia. Vision: R. E.+2.5=0.1; L. E.+2.5=3/50. Discs and maculas N. A. D. No peripheral changes. (O—n).

F. 25 a TI. ♂ *b. 1928*

Congenital amblyopia. Retinochoroiditis. *1935:* Vision: R. E.=0.1/60; L.E.= =0.2/60. Pupils of medium size, scarcely react to light. Temporally in both lenses, slight radial opacities. More peripherally in fundi, inappreciable pale foci; fundi otherwise normal. — *1938*: vessels narrow but discs otherwise normal. — *1946*: Vision as earlier. No nystagmus. Keratoconus with central corneal opacity, although not dense, in right eye. Vessels, macula and periphery N. A. D. (O—n). — Diabetes since 1936; insulin therapy. Epileptic seizures since 1939.

F. 25 b TI. ♀ *b. 1930*

1935 (S—l Hospital): Nystagmus both eyes. Pupils reacted to light. Medias and fundi normal. Did not see objects presented, *e. g.* pocket torch. Walked into furniture in her path. — Bilateral degeneration of the retina (Degeneratio retinae). *1937*: Vision: R. E. and L. E.=Hand movements. Pupils reacted only slightly to light. Discs normal. Sparse pigmentation. — *1946*: Frequent, slight,

jerky eye movements. Discs, vessels, maculas and periphery N. A. D. — *1948:* Status quo. (O—n).

F. 26 a TI. ♂ b. 1923

Bilateral retinochoroiditis. *1930*: Vision: R. E. and L. E. = 0.6/60, finger counting at 0.6 m markedly excentrically. Large rigid pupils. Large foci of pigment scattered over whole fundus. — *1938*: Vision: R. E. and L. E. = 0.25/60 far temporally. — *1956*: Vision: R. E. = Hand movements; best distinguished temporally but no apparent limitation of visual field; L. E. = Hand movements. Pupils reacted normally. Media: bilateral keratoconus with a few small, grey corneal opacities. Visible part of both lenses clear. Fundi: numerous, fairly large clumps of pigment over greater part, as well as smaller, pale atrophic foci. Both maculas extremely difficult to see, but they did not seem to contain so much pigmentation. Discs perhaps somewhat pale and vessels sligthly narrow. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 26 b TI. ♀ b. 1925

Bilateral retinochoroiditis. *1931*: Vision: R. E. = 1/60 excentrically; L. E. = = 1.5/60. *1932*: Medias clear. At any rate left disc pale. Sparse and inappreciable choroiditic changes. — *1937:* Vision: R. E. = 0.3/60; L. E. = 0.25/60. Moderate limitation of visual fields for hand movements. — *1939:* Pigment as in retinitis pigmentosa but in macula as well. — *1942*: Vision: R. E and L. E. = = Finger counting at barely 10 cm. Very small visual fields for hand movements. Both medias clear.

F. 27 a TI. ♂ b. 1919

Congenital amblyopia. *1928*: Vision R. E. = Perception of light; L. E. = 1/60. Marked nystagmus and some photophobia. Pupils did not react. Colour blind. No fundus changes. — *1931*: Bilateral keratoconus, marked photophobia, corneal opacity in right eye, otherwise as earlier. — *1955*: Vision: R. E and L. E. = 1/50. Pupils reacted well to light. Distinct keratoconus, very slight opacities in right cornea, none in left. Fundi: no definite pigmentary changes. Discs somewhat blurred and yellowish. Vessels slightly narrowed. (O—n).

F. 28 a TI. ♀ b. 1938

Congenital amblyopia. *1943*: Vision: R. E. and L. E. = Hand movements, could not count fingers. Slow, irregular nystagmus. Medias normal. Discs not pale, nasal margin blurred. Whole fundus covered with fine yellowish-black, fairly ill-defined dots. No vascular changes. — *1945*: Status quo. — *1946*: Irregular eye movements. Discs, vessels and maculas N. A. D. Periphery partly strikingly black-pigmented. Downwards, a few groups of small round or triangular yellowish spots. — *1954*: Discs somewhat pale, otherwise status quo. Patient was examined at Eye Department, Sundsvalls Hospital in 1940 (at 2 years of age): medias, nothing pathologic; fundi normal.

F. 28 b ♂ b. 1949

Examined at O—k Hospital at age of 6 months. *1950*: Vision seemed to be very poor. Was able to focus on ophthalmoscope and source of light. Discs

pale pink with somewhat unclear details, margins slightly blurred but no protrusion. Arteries extremely narrow. No light reflex visible in the macula; colour yellow-dotted with no distinct centre. Formations resembling peppercorns scattered in the periphery. Diagnosis: tapetoretinal degeneration. — *1956:* Vision: R. E. and L. E. = Hand movements. Pupils reacted to light. No nystagmus but some irregular eye movements. Corneas N. A. D. Medias clear. Central part of fundi of normal colour; macular reflex lacking, maculas otherwise entirely normal. In periphery, numerous, small round yellowish atrophies, often with black pigment in the margin. A number of small black pigmented spots and a few somewhat larger irregularly shaped ones also present. Discs somewhat rounded and blurred, arteries narrow. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 29 a TI. ♀ b. 1911

Bilateral retinochoroiditis. Vision: R. E. and L. E. +3>2/60. *1920*: Nystagmus: Speck-like opacities of the vitreous, in the right eye globular, large grey ones. Fundus strewn with masses of pigmentary foci; in the macular region a yellowish focus the size of a disc. Moderate retinitic atrophy of the discs. — *1956:* Defective sight since birth, somewhat worse with age. Vision: R. E. and L. E. = Perception of light. Irregular eye movements. Pupils reacted faintly to light. Corneas normal. In the left lens, a round, central posterior cortical cataract which did not prevent inspection to any great extent; a larger cataract in the right lens. Fundi: the right was difficult to see but did not appear to differ from the left. The left fundus had a somewhat pale disc with narrow vessels. Only slight changes in the macular region; colour fairly yellowish with vessels. Only slight changes in the macular region; colour fairly yellowish yellow colour, but with numerous punctate and linear black pigmentations. In some places they were confluent in large, irregular units. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 30 a TI. ♀ b. 1895

Bilateral retinochoroiditis. *1908:* Vision: R. E. and L. E.>4/60. — *1946:* Able to distinguish between light and darkness. Just able to go about alone. Finger counting 1 m?. Irritated by sunlight. Pupils reacted distinctly but weakly to light. In both fundi, scattered black streaks of pigment; irregular small, black pigmented spots. (A—m).

F. 31 a TI. ♂ b. 1891

Optic nerve atrophy. *1905:* Vision: R. E. and L. E. = 0. — *1946:* Could not distinguish between day and night or between light and darkness, but irritated by strong sunlight. Pupils did not react to light. Total, bilateral cataract. No keratoconus. Fundi could not be inspected on account of cataract. Blindness observed at 7 months of age. (A—m).

F. 31 b TI. ♀ b. 1908, d. 1919 of diphtheria

Bilateral retinochoroiditis. *1918:* Vision: R. E. and L. E. = 0. Moreover, stated to be »born blind, with optic nerve atrophy like her brother». Fundi: masses

of small pigmented foci scattered over the fundus; in macular region, an enormous atrophic focus, excavated.

F. 32 a (De). ♂ b. 1911, d. 1946 of renal disease

Greatly impaired sight since birth. Struggled through ordinary elementary school; according to teacher could only see large letters and those on blackboard, could not distinguish lines in exercise books. Could just get about alone at beginning of schooling, subsequently exacerbation. — *1946*: Vision greatly impaired; could not distinguish people directly beside him at dusk; could probably just get about alone in daylight. No definite changes apparent in discs; vessels somewhat narrow. Small black grains of pigment over whole fundi, largest number in periphery. — Neurologic examination showed nothing pathologic. Mental state: marked dysphoria, depression of moderate degree. Intelligence normal. (A—m).

F. 32 b (De). ♀ b. 1915, d. 1948

According to teacher and parish records had poor sight, worse than that of brother; was regarded as virtually blind. Not encountered on visit to home. (A—m).

F. 33 a (De) Up Vä. ♀ b. 1893

Poor sight since birth. Attended School for Blind in Upsala, Nynäshamn and Växjö. — *1946*: Vision: R. E. and L. E. = Perception of light. No light reflex. No distinct changes in discs. Small black round pigmented spots over whole fundi, most peripherally but centrally as well. No keratoconus. (A—m). — *1956*: Defective sight since birth, but as a child and young adult could read in a strong light; no longer possible. Had difficulty in seeing in the dark. She stated that there had been limitation of the visual fields, which could presumably be assessed better when she was younger. Vision: R. E. and L. E. = = Hand movements. No noteworthy eye movements. Pupils reacted best to central, and not at all to weak peripheral illumination. Owing to the defective vision, the visual fields could be estimated only by testing with a narrow beam from various directions. This showed the outer limits to range between 10° and 20° (examination with slit lamp). Cornea of both eyes N. A. D. Central, posterior cortical cataract in lens of both eyes. The fundi could be inspected fairly well through the periphery of the lens. Discs blurred, reddish-grey and small; vessels thread-like. Fundi yellowish-red, with numerous, chiefly small and medium-sized round spots of pigment. Others, also fairly small, irregular in shape. Pigmented spots also present in both macular regions, but not so close together. Round only at this site. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 33 b (De). ♂ b. 1898

1946: Poor sight since birth. Struggled through ordinary elementary school with great difficulty on account of defective vision. Now only able to distinguish between light and darkness. Gets about out-of-doors with the help of touch and hearing. Fundi exhibited similar picture to that in sister (33 a),

except that irregularly shaped pigmented spots were also present. No cataract or keratoconus. (A—m). — *1956*: Defective sight since birth. Could not read fine print at school. Twilight vision not worse, but rather better than daylight vision. Some limitation of visual fields. Vision: R. E.=0; L. E.=Hand movements. Left pupil reacted to light, although weakly; right did not react. No noteworthy eye movements. Visual fields of left eye could be evaluated to some extent by throwing a narrow beam of light into it. Greatly limited (about 10°). Cornea of both eyes N. A. D. Central, irregularly rounded posterior cortical cataract in lens of both eyes. The fundi could be seen fairly well. The reflex was yellowish-red. Discs somewhat pale, and blurred at margins; vessels narrow. Fairly numerous black pigmented spots over whole of both fundi; mostly small or medium-sized, round. Only occasional pigmented spots in macular region of both eyes, none centrally. (O—n). *1956*: *ERG* of both eyes extinguished.

F. 33 c (De). ♀ *b. 1906, d. 1936 of renal disease*

Greatly impaired sight since birth in similarity to sibs, but was considered to see relatively best of them. She also struggled through the local elementary school.

F. 33 d (De) TI. ♀ *b. 1911, d. 1944 of pulmonary tuberculosis*

Retinochoroiditis. *1920*: Vision: R. E.=3/60; L. E.=2/60. Discs not strikingly pale but arteries narrow. Maculas normal. Peripherally, both coarse and snuff-like pigment, as well as larger choratrophic foci.

F. 34 a (De) TI. ♂ *b. 1931*

Bilateral degeneration of the retina. *1938*: Vision R. E.+1.75=4/50; L. E.+ ±1.75=0.1. Medias clear. Discs normal, arteries narrow, maculas normal. Plentiful masses of granular pigment with small pale areas round the whole periphery. Severe hemeralopia. Small visual fields. (Retinitis pigmentosa diagnosed by provincial health officer in 1938.) — *1940*: Vision R. E.=2/60 L. E.= =4/60. Could not follow class for partially sighted, owing to inability to fixate. — *1946*: No nystagmus. Discs normal, arteries somewhat narrow, maculas normal. Periphery distinctly small-spotted; alternating dark and yellowish-white spots (pepper and salt). Great limitation of visual fields. (O—m). — *1956*: Defective sight since birth, no marked change. Divergent strabismus of moderate degree. No noteworthy eye movements. Pupils reacted to light. Vision: R. E.=Finger counting at 40 cm, L. E.=Finger counting at 60 cm; centrally or paracentrally. Visual fields limited temporally to 20—30°, nasally to similar values; upwards and downwards not as much. (Owing to the poor visual acuity, only approximate values could be obtained, *e. g.* by hand movements.) Corneas and medias clear. Fundi of normal colour. Discs normal. Vessels normal, except that a few arteries were strikingly narrow and of somewhat uneven caliber. Scattered, chiefly in the periphery, small black or grey pigmented foci, often surrounded by a lighter atrophic zone. In some places, larger foci of pigment as well, not particularly close, irregularly angular in shape. In a few places, deposits of pigment on veins. In macular regions, only

inappreciable displacement of pigment; in the right fovea those of the first type described above were seen. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 35 a Tf. ♀ *b. 1937*

Congenital amblyopia. *1946*: Vision R. E.=Hand movements; L. E.=1—2/50. No nystagmus. Discs, vessels, maculas and periphery N. A. D. (O—n). — The patient was not moved up into the elementary school, on account of dullness; she was subsequently referred to special-class instruction in Lund. — *1954*: Vision: R. E.=1/60; L. E.=0.5/60. Pale, atrophic discs, otherwise nothing pathologic. (Lund).

F. 36 a TI. ♂ *b. 1926*

Bilateral retinochoroiditis. *1934:* Vision: R. E.+2—90°=4/50; L. E.+2——90°=0.1. Nystagmus since birth. Retinitic atrophy of discs, but no definite foci in either fundus. — *1940:* Vision: R. E. and L. E.=1/50. — *1946:* Night blindness; just able to get about alone in daytime, medias clear. Fundi markedly dark-grey pigmented, with occasional radial pigmented foci, resembling bone corpuscles. Vessels narrow. No definite pallor of discs. (L—n). — *1956*: Poor sight since birth. No definite change in vision during the years. Vision: R. E.=Hand movements; L. E.=Finger counting at 1—2 m. Visual field good (hand movements). Corneas N. A. D. Cataract in posterior lens cortex of both eyes, only slightly disturbing inspection, polar, and spoke-formed. Fundi: discs somewhat pale, vessels narrow. Centrally, no definite changes. In the periphery, numerous greyish spots and pigmented spots; some fairly small and punctate, some irregular, others resembling bone corpuscles. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 36 b TI. ♂ *b. 1934*

Impaired sight noticed soon after birth. Nystagmus since birth. Attended Eye Department, Falu Hospital, when patient was 4 years old. Pupils reacted to light. Discs somewhat pale, vessels narrow. Fundi atrophic (Leber's disease?). — *1941*: Bilateral degeneration of the retina. (Degeneratio retinae o. a.) Vision: R. E.=1/60; L. E.=1.5/60. Visual fields for hand movements fairly normal. Nystagmus. Pupils reacted sluggishly. Narrow retinal vessels. Yellowish discs. — *1946:* No nystagmus. Discs normal, arteries narrow, maculas normal. Periphery normal. Vision: R. E.=1/50; L. E.=1.5/50. — *1951*: Vision: R. E.=1/50; L. E.=1.5/50. Fundi: periphery somewhat greyish-white spotted. Discs pale. Arteries narrow. (O—n).

F. 37 a Tf. ♂ *b. 1937*

1944: Vision: R. E.=0.1; L. E.=0.2. Difficulty in fixating. Gaze turned involuntarily, sometimes in one direction, Sometimes in another. Medias clear. Discs pale, otherwise normal. — *1946*: Congenital amblyopia. Vision: R. E.=——0.1—0.2; L. E.=0.2. No nystagmus but see above. Discs, vessels, both maculas and periphery N. A. D. (O—n).

F. 38 a (Su) TI. ♂ b. 1924

Bilateral retinochoroiditis. *1933:* Vision: R. E. and L. E.=Hand movements. Sparse opacities of vitreous. Retinitic atrophy; peripherally, both branched pigmented and small, choratrophic white foci. Marked undulating eye movements. *1940* (TI): As earlier, numerous pigmented foci. — *1946*: Constant eye movements and simultaneous, obsessive-neurotic mimic movements. On both sides, numerous pigmented foci, small, irregular, over whole fundus, most peripherally. Discs seemed to be normal. Vision: R. E. and L. E.=Perception of light. (A—m). — *1952*: *ERG* of both eyes extinguished. — *1956*: Since birth, only able to distinguish between light and darkness; no marked change. Vision: R. E.=0; L. E.=Uncertain perception of light. Pupils did not react to light. Irregular eye movements. Distinct bilateral keratoconus; small paracentral opacity in left. Both lenses clear. Fundi: reflex of ordinary colour. Discs somewhat pale and vessels somewhat narrow. No marked changes in either macula. In rest of both fundi, numerous black pigmented spots, often confluent and irregularly shaped, but mostly triangular. (O—n).

F. 39 a (Su) TI. ♂ b. 1937

1938: Difficult to examine. Very defective sight. No objective findings (Eye Department, K—d Hospital). — Amblyopia congenita. *1944*: Vision: R. E. and L. E.=0. Pupils did not react to light. Fundi: macular regions deficient in pigment. Discs grey with indistinct markings. — Bilateral retinochoroiditis. *1946*: Some irregular eye movements. Markings of disc extremely blurred. Vessels and macula normal. In the periphery, numerous small yellowish spots, alternating with small accumulations of pigment. Right eye and left eye similar. (O—n).

F. 40 a (Su) TI. ♂ b. 1916.

Bilateral retinochoroiditis. *1923:* Vision: R.E. and L.E.=0. Masses of yellow-white foci with flecks of pigment peripherally. Usual retinochoroid degeneration type. Inappreciable incipient cataract peripherally. — *1930*: Bilateral keratoconus. — *1956*: Vision: R. E. and L. E.=0. Pupils did not react to light. Irregular eye movements, no nystagmus. Marked keratoconus with small, central corneal opacities. Lens: moderate right, dense left cataract. Fundi: only the right could be inspected. The macula seemed to be normal. Disc somewhat pale, vessels somewhat narrow. Colour of fundus normal. In its peripheral parts, a moderate number of small, black pigmented spots, punctate or in streaks. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 41 a (Su) TI. ♂ b. 1874, d. 1923 of organic heart disease

Bilateral optic nerve atrophy (1883). Only notation »totally blind». — According to sibs, he was »blind» from birth, but was able to distinguish light from darkness. (A—m).

F. 41 b (Su) TI. ♂ b. 1892

Bilateral optic nerve atrophy. *1904*: »Perception of light in one eye, 0.1/60 in the other.» — *1946*: Treated for manic-depressive psychosis; recovered after

electroshock therapy. Extract from record: Bilateral keratoconus. Totally blind. Pupils did not react to light. — *1955*: Mentally and neurologically, nothing abnormal. Stated that he was »born blind». Able initially to distinguish between light and darkness. Still irritated by strong sunlight, but less than formerly. Pupils reacted distinctly to light. Rolling eye movements. (A—m). — *1955*: Vision: R. E. and L. E.=Perception of light. Pupils reacted to light. Visual fields could not be evaluated, but patient stated that he could judge where a light was lit. Bilateral keratoconus with central corneal opacities, most developed in left eye. Dense cataract in left eye; in right eye, cataract extending only to lens. Left fundus not visible. Right fundus had reddish-yellow colour. No large pigmentations were present, but details could not be seen on account of medial opacities. (O—n).

F. 42 a TI. ♂ b. 1922

1925: Pupils did not react to light. Nystagmus. No pigmented spots visible (Eye Department, K—d Hospital). — Bilateral retinochoroiditis. *1929*: Vision: R. E. and L. E.=0. »Only periphery of fundus visible, in which a number of choratrophic foci were present.» — *1930*: No evident changes in discs. Retinal vessels slightly constricted. Peripherally, some coarse granularity of pigment (resembling snuff) and slight pallor. — *1940*: Some pallor of discs. — *1946*: Pupils did not react to light. Only faint perception of light when testing with beam of light. Marked bilateral keratoconus; scattered, irregular pigmented spots in both fundi. Discs pale, vessels narrow. (L—n). *1956*: Vision: R. E.=Perception of light?; L. E.=Perception of light. Able to perceive very strong general illumination, probably with left eye only. Pupils could not be observed to react to light. Marked keratoconus with small, central slit-shaped opacities. Lens of both eyes clear. Fundi: discs pale, vessels extremely narrow. Plentiful black pigment in fundi; punctate and in form of streaks, as well as of irregular shape, and sometimes in shape of bone corpuscles. Some smaller spots were also present in both macular regions, which otherwise showed no visible changes. The basic colour of the fundi did not differ distinctly from the ordinary colour. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 42 b TI. ♀ b. 1932

Bilateral degeneration of the retina. *1939:* Vision: R. E. and L. E.=0. Medias clear. No pallor of discs, but vessels extremely narrow. Peripherally, masses of small pigment clumps and paler small foci. — *1946*: Irregular eye movements. Discs somewhat reddened. Arteries narrow. Maculas normal. In periphery, not only halfway but furthest out as well, small, irregular black pigmented spots, some of the bone-corpuscle type, alternating with small yellowish dots. Right and left eye similar. (O—n). — *1950:* Status quo.

F. 43 a TI. ♀ b. 1896

Optic nerve atrophy. *1903:* Vision: R. E. and L. E.=0. — *1946:* L. E. total cataract; R. E. scattered, irregular pigmented spots. (L—n). — *1955*: Had never been able to distinguish between light and darkness. Vision: R. E. and L. E.=0. Pupils did not react to light. No noteworthy eye movements. Dense cataract in left eye; in right eye, cataract centrally in posterior cortex. Synchy-

sis scintillans in right eye. Left fundus could not be seen; right fundus difficult to see. Numeros, small round pigmented spots and larger irregular ones were present. Fundus reddish-yellow. Disc could not be seen. Vessels narrow. (O—n).

F. 43 b TI. ♀ b. 1902

Bilateral retinochoroiditis. *1909*: Vision: R. E. and L. E.=0. After attending primary school and three classes of the elementary school at Tomteboda, she was sent to Lund as »of subnormal intelligence». At present, she is somewhat childish and dull; within physiologic limits. Diagnosis in Lund: optic nerve atrophy and retinochoroiditis. — *1955*: Vision: R. E. and L. E.=0. Pupils did not react to light. No noteworthy eye movements. Distinct, bilateral keratoconus, with small opacities in the right cornea. Fundi: discs sallow. Vessels very narrow. Colour of fundi reddish-yellow. Both fundi strewn with pigmented spots of various shapes: small round ones, and both small and large reticular and stellate spots. Both maculas were evenly pigmented. The smallest number of pigmentations were present nasally. (O—n).

F. 44 a TI. ♀ b. 1917

Retinitis pigmentosa. *1928:* Vision: R. E. and L. E.+8=2/60. Visual fields small. Pupils reacted sluggishly. Discs not markedly pale; margins blurred and arteries narrow. Otherwise, typical picture but pigment present centrally as well, partly in drifts. — *1932—36*: Diagnosis changed by same examiner to bilateral retinochoroiditis. Vision: R. E. and L. E.=Hand movements. — *1946*: Vision: R. E.=0; L. E.=Perception of light. Total cataract in right eye. In left fundus, numerous large, black pigmented foci as well as small ones. Disc pale. Vessels narrower than usual. (L—n). — *1956*: Defective sight since birth, further decrease since about 10 years of age. Vision: R. E. and L. E =Perception of light. Pupils reacted to light. Slow nystagmus. Marked keratoconus with small central opacities. Dense, shrunken cataract bilaterally. Fundi could not be inspected. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 44 b TI. ♀ b. 1922

Bilateral retinochoroiditis. *1929*: Vision: R. E.=0.5/60; L. E.=1/60. Lively nystagmus. Dust-like opacities of the vitreous. Discs slightly pale and margins blurred. Numerous round foci of pigment with lighter surroundings. Moderate limitation of visual fields for hand movements. — *1932*: Vision: R. E.=0.5/60; L. E.=0.7/60. — *1946*: Opacity of the vitreous in left eye, otherwise, black pigmentations as in patient's sister. (L—n). — *1956*: Defective sight since birth, not definitely worse with age. Vision: R. E.=Hand movements; L. E.=Perception of light. Pupils reacted to light. Divergent strabismus in left eye. Inconstant nystagmus. Corneas clear. Slight keratoconus of right eye. Central, posterior cortical cataract in right lens; left lens clear. Very slight opacities of the vitreous of right eye, numerous such opacities in the left, one of them obscuring the disc. Fundi: right disc blurred and seemed to be covered by a greyish-white mass; left obscured by a greyish-white opacity of the vitreous. Those vessels that could be seen seemed to be unchanged. Macular regions

difficult to see, but they did not seem to be markedly altered, although possibly somewhat pale and atrophic. Below the disc-macular region of the right eye, a large, pale atrophic area (2—3 times the size of the disc). Pale, atrophic foci also visible in the periphery of the fundus, but were not marked. At this site, also numerous, round, greyblack pigmented spots, as well as a lesser number of smaller, irregularly shaped black pigmentations. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 45 a Tl. ♀ *b. 1899, d. 1947*

Bilateral congenital amblyopia. *1910*: Vision: R. E. and L. E.=2/60. Totally colour blind; »defective sight since birth, photophobia. Able to get about alone but not in sunlight».

F. 46 a Tl. ♀ *b. 1894*

Bilateral retinochoroiditis. *1904*: Vision: R. E and L. E.=Perception of light. »Same changes as in brother.» — Irregular eye movements. Vision: R. E. and L. E. =0. Pupils do not react to light. Corneae clear, slight keratoconus on right eye. Bilateral dense cataracts. (O—n).

F. 46 b Tl. ♂ *b. 1895*

Bilateral central retinochoroiditis. *1904*: Vision: R. E. and L. E.=Perception of light. Large atrophic focus of mottled appearance. — *1956*: As a child, able to see large letters; can now only distinguish light from darkness. Vision: R. E. and L. E.=Perception of light. Pupils reacted slightly to light. Corneas clear. Dense bilateral cataract. Peripherally, a small area of the right fundus could be seen; mainly round, black pigmentations of medium size were visible. (O—n). — *1956*: *ERG* of both eyes extinguished. *1956*: Retinochoroiditis right eye (and left eye?) and bilateral cataract. On admission to Eye Clinic, Karolinska Sjukhuset; right eye: perception of light, no localization. Marked opacities of the lens. Glimpses of white foci peripherally; otherwise, the fundus could not be evaluated. Left eye: perception of light, no localization. Marked opacities of the lens. Fundus could not be evaluated. Operation right eye: intracapsular extraction of lens. Postoperative course uneventful. Right eye after operation: clumps of pigment, as well as punctate atrophies and blotched ones spread over the whole fundus. No definite improvement in vision postoperatively. (Eye Clinic, Karolinska Sjukhuset).

F. 47 a Tf. ♀ *b. 1910, d. 1918 of diphtheria*

Bilateral optic nerve atrophy. *1917*: Vision: R. E. and L. E.=0. No other notations. When her home was visited, her father stated that defective vision was noticed a few months after birth. He said that she was somewhat »temperamental and difficult to bring up» but there was nothing else noteworthy. Died after one year at Tomteboda. (A—m).

F. 47 b. ♂ *b. 1917, d. 1919 of tuberculous meningitis*

According to the father, blindness was noticed soon after birth. He developed normally in other respects until he became acutely ill and died at the age of $2\,^1/_2$ years.

F. 47 c TI. ♂ b. 1922

Bilateral congenital amblyopia. *1930*: Vision: R. E. and L. E.=0. No objective changes, except that in the upper part of the left eye the pigment was somewhat coarsely granular. Discs and vessels normal. — *1932*: Status quo. — *1924*: Examination at Serafimerlasarettet: Vision: R. E. and L. E.=0. Diagnosis: congenital degeneration of the retina. — *1955*: Stated in the admission certificate (1930) to be »somewhat mentally retarded, with coreatic (?) twitches in arms and fingers». The patient went through the elementary school with average marks, and subsequently managed his work without difficulty. Neurologically: N. A. D. Some rocking movements of an obsessional-neurotic nature when he became eager; no choreatic or other neurologic symptoms. No history of chorea: healthy apart from usual respiratory tract illnesses. Mentally normal. (A—m). — *1956*: Vision: R. E. and L. E.=0. Pupils did not react to light. Irregular eye movements. Medias clear. Fundi of ordinary colour and appearance. Discs and vessels normal. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 48 a TI. ♂ b. 1886, d. 1929 of carcinoma of the stomach

Optic nerve atrophy. *1899*: Vision: R. E. and L. E.= Perception of light, not finger counting. — *1911*: Fundi: both sides strewn with black spots. Retinal vessels very narrow. Pupils did not react to light. (N—g Mental Hospital; schizophrenia with onset att 22 years of age.)

F. 48 b TI. ♀ b. 1893, d. 1906 of appendicitis and peritonitis

Bilateral retinochoroiditis. *1905*: Vision: R. E.=0.5/60; L. E.=1/60.

F. 48 c TI. ♀ b. 1897

Bilateral retinochoroiditis. *1905*: Vision: R. E.=Perception of light; L. E.= =0.5/60. — *1956*: Perception of light as a child, not in recent years. Vision: R. E. and L. E.=0. Pupils did not react to light. Corneas normal. Fairly dense bilateral cataract. Fundi could not be seen. Nystagmus and divergent strabismus. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 49 a TI. ♂ b. 1921

Bilateral retinochoroiditis. *1928:* Vision: R. E. and L. E.=0. Discs completely normal. Central parts and otherwise N. A. D. Peripherally, masses of greyish foci and snuff-like pigment. Eyes sunken. — Blindness noticed at a few months of age. Examined at 9 months at Eye Department, Sabbatsbergs Sjukhus: Pale, small foci peripherally and snuff-like pigment. — *1955*: Since 1937, occasional epileptic seizures of unknow cause, controlled by medication. Period of depression in 1940—41; now entirely recovered. Neurologically: N. A. D. Intelligence above normal; sum of marks 15 as compared to class median 9.9. Manages fairly well socially; gifted technically. (A—m). — *1955/6*: Vision: R. E.=Perception of light, weaker than left; L. E.=Perception of light. Perception with long reaction time in both eyes. Pupils reacted slightly to light, the left better. Keratoconus with small macula centrally in right cornea; left cornea clear. Medias otherwise clear. Fundi: discs somewhat blurred and

yellowish. Vessels somewhat narrow. Peripherally, not centrally, moderate number of small round pigmented spots and angular ones as well. Fundi of usual colour. (O—n). *1955*: *ERG* of both eyes extinguished.

F. 50 a (85) TI. ♂ b. 1921

Bilateral congenital amblyopia. *1932*: Vision: R. E. and L. E. = 0.1. Nystagmus since first year of life. No definite fundus changes. — *1931* (Akademiska Sjukhuset, Uppsala): Skiascopy: R. E. and L. E. ± 0. Vision = 0.1; no definite fundus changes. — *1955*: Nystagmus on fixation. Pupils reacted well to light. Medias clear. Visual fields good. Fundi: somewhat myopic; deficient in pigment, with slight conus formation at the discs, which had the appearance usual in myopia, possibly slightly blurred. Vessels of usual appearance. No displacement of pigment. Vision: R. E. — 3 = 0.1; L. E. — 3 = 0.2, binocularly 0.3. The impairment of vision cannot be explained by error of refraction. (O—n). — *1955*: *ERG*: R. E. Normal; L. E. Probably normal. *Flicker ERG*: pathologic. (G. Karpe).

F. 51 a (!) TI. ♀ b. 1917

Bilateral retinochoroiditis. *1926:* Vision: R. E. = 2—4/60; L. E. = 5/60—0.1. (Earlier recorded as »retinitis pigmentosa»; crossed out and replaced by above diagnosis.) Lively nystagmus. Small pupils, not reacting to light. Numerous fine opacities of the vitreous. Retinitic atrophy of discs. Pigment as in retinitis pigmentosa but foci in macula as well. — *1935:* Vision: R. E. = 1/60; L. E. ≤ 1/60. Visual fields minimal. Pupils reacted to light. Very slight opacity in anterior lens cortex. — *1941*: Vision: R. E. = Hand movements; L. E. = Perception of light. Started to attend ordinary elementary school but could never read ordinary books, had books with large type. Glimpsed schoolmates but could never distinguish their features; recognized them by clothing and size. Her parents did not know about Tomteboda; a teacher in the 3rd class arranged for her admission. Sight gradually deteriorated; at 18—20 years of age could barely get about alone. — *1955*: Vision: R. E. and L. E. = Perception of light and localization temporally, downwards and upwards, not nasally. Pupils reacted to light. Visual fields hard to assess; seemed to be limited nasally. Could be tested only by strong direct illumination of eye. No noteworthy eye movements. Cataract bilaterally in posterior cortex. Discs pale, not yellowish, fairly sharply defined. Vessels narrow. Colour of fundi reddish-yellow. Plentiful, black confluent pigment round whole periphery. Only in macular regions was the pigmentation inappreciable; here, only some round spots were seen. (O—n).

F. 52 a (101) TI. ♂ b. 1932

Bilateral congenital amblyopia. *1939*: Vision: R. E. and L. E. = 0. No marked nystagmus. Objectively, no conspicuous changes could be observed. — *1946*: Some nystagmus. In periphery of right lens, narrow streaks of cataract. In left eye, a few dense opacities almost centrally in posterior lens capsule. Disc and macula of both eyes N. A. D. In periphery of fundus, alternating dark and yellowish small spots (pepper and salt). (O—n).

F. 53 a TI. ♀ *b. 1919*

Bilateral amaurosis congenita. *1931*: Marked nystagmus but no changes in medias or fundi. *1946*: Vision: R. E. and L. E. = 0. Keeps her eyes relatively still. Bilateral keratoconus. No cataract. No certain pathologic fundus changes, but they are hard to assess on account of keratoconus. (A—m). — *1956*: Vision: R. E. and L. E. = 0. Pupils did not react to light. Marked keratoconus with small opacities at the apex. Both lenses clear. Fundi: yellowish-red with small, pale atrophic areas and small, round spots of pigment. Maculas seemed to be normal, but definite evaluation was prevented by keratoconus. Discs somewhat pale and vessels somewhat narrow. (O—n). — *1956: ERG* of both eyes extinguished.

F. 54 a (*55*). ♂ *b. 1925*

Bilateral congenital amblyopia. *1937*: Marked horizontal nystagmus. Pupils reacted somewhat sluggishly to light. Vision: R. E. and L. E. — 7 = Finger counting at 3 m. Skiascopy: R. E. —7.5 10°; L. E. 4.5 100°. Colour blind; could not manage Ishihara's or Boströms tables. Discs pale, fundi N. A. D. (S. B—t). — *1940* and *1943:* Status quo. (S. B—t). — *1952:* Vision: R. E. and L. E. — 7 = 0.1. Concentric limitation of visual fields. Unable to see colours. Otherwise, status quo (S. B—t). — *1956*: Defective sight since birth; no subsequent change. Considerable nystagmus-like eye movements, elicited particularly on any attempt at fixation. Vision: R. E. — 6—2 cyl 15° ≤ 0.1; L. E. — 6—2 cyl. 165° = 0.1.

Medias and corneas clear. Fundi: somewhat myopic, otherwise entirely normal. No pallor of discs. Vessels of ordinary width. No displacement of pigment could be detected. (O—n). — *1956*: *ERG* of both eyes subnormal.

F. 54 b (*55*). ♀ *b. 1928*

Bilateral congenital amblyopia. *1935*: Marked nystagmus; inability for central fixation. Photophobia. Vision: R. E. = Finger counting at 0.5 m uncertain; L. E. = Finger counting at 3.5 m uncertain. Astigmatism: R. E. 4D ax. 105°; L. E. 4D ax. 75°. Skiascopy: R. E. +3.5 110°; L. E. +3.5 60°. Pupils reacted normally to light. Media of both eyes clear. Fundi: discs pale, vessels narrow. (S. B—t). — *1940*: Status quo. (S. B—t). — *1946*: Vision: R. E. —3 cyl ax. 20° = 0.2/60; L. E. —3 cyl ax. 60° = 0.2/60. (S. B—t).

F. 54 c (*55*). ♀ *b. 1943*

1944: Photophobia. Vision could not be tested. Skiascopy could not be performed. Marked nystagmus. Only glimpses of the fundi could be seen. (S. B—t). — *1948:* Vision: R. E. and L. E. = 0.4 at 1.5 m. Skiascopy +5. Medias clear. Pupils reacted normally. Fundi: discs pale, otherwise N. A. D. (S. B—t). — *1952:* Vision: R. E. + 1 = 0.2 at 1.5 m; L. E. + 1 = 0.3 at 1.5 m. Small polar cataract posteriorly on right side. Otherwise status quo. (S. B—t).

F. 55 a (*54*) *TI.* ♂ *b. 1933*

Congenital amblyopia. *1943:* Vision: R. E. and L. E. + 2 = 3/50. No actual nystagmus, but irregular, casting eye movements. Disc, vessels, macula and periphery of both eyes N. A. D. — *1948*: Status quo. *1956*: Vision: R. E. =

= ± 0—2.0 0° cyl=4/50; L. E. = — 0.5—1.5 0° cyl=3/50. Pupils reacted normally. Considerable nystagmus-like movements, elicited in particular immediately on any attempt at central fixation. Divergent alternating strabismus. Media clear. Cornea N. A. D. Fundi: small conus formations at discs. Discs otherwise of usual colour; no pallor. Vessels of ordinary width. No pigmentations visible. Whole fundus picture consistent with slight myopia. (O—n). — *1956*: *ERG* of both eyes impossible to evaluate owing to nystagmus.

F. 56 a TI. ♀ b. 1904

Bilateral retinochoroiditis. *1917:* Vision: R. E. and L. E. = 2.5/50. Sparse opacities of the vitreous. Moderate retinitic atrophy of discs. Whole of both fundi strewn peripherally with small, yellowish-white choratrophic foci. Sparse, finely branched pigment. — *1946*: Just able to get about alone. Finger counting 1 m? No keratoconus or cataract. Over whole of both fundi, sparse round and irregularly shaped black pigmentations. (A—m).

F. 57 a TI. ♀ b. 1912

Congenital amblyopia. *1924*: Vision: R. E. and L. E. = Perception of light. No objective changes. — *1925*: Opaque spokes in both lenses. — *1926*: Vision: R. E. and L. E. = Perception of light. Bilateral keratoconus and increased opacities in lenses. — *1946*: Vision: R. E. and L. E. = Perception of light. Marked bilateral keratoconus. Details of fundi uncertain, owing to keratoconus and constant eye movements, but apparently normal. (A—m). — »Blind since birth»; statement from 1919 of light perception only. *1956*: Sight unchanged since childhood. Vision: R. E. and L. E. = Perception of light. Pupils reacted well to light. Visual fields seemed to be normal. Marked keratoconus with some central opacities, chiefly in right eye. Lenses clear. Fundi: discs somewhat pale, vessels somewhat narrow. Only very few pigmented spots; small and round or slightly streaked. Neither macula could be definitely evaluated, but no distinct changes seemed to be present. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 58 a TI. ♀ b. 1913, d. 1943 of subarachnoid haemorrhage

Bilateral retinochoroiditis. *1924*: Vision: R. E. and L. E. = 0. Blindness detected at 11 months of age, when she was hospitalized for another illness. In posterior cortex of left lens, a few sectors. Medias otherwise clear. Discs and central parts of fundi N. A. D. Peripherally, small choratrophic foci and partly branched pigment. — *1929*: »Keratoconus appeared.» Otherwise status quo.

F. 59 a TI. ♀ b. 1937

Bilateral retinochoroiditis. *1946:* Vision: R. E. and L. E. = 0. Marked, irregular eye movements. Discs somewhat pale, chiefly the left. Vessels narrow, no definite changes in maculas. Patient difficult to examine. In periphery, not especially far out, some pigmented foci of disseminated choroiditis type. Thin, peripheral, spoked opacities of the lens. A few dense, floating opacities in the vitreous. Right and left eye similar. — *1954*: Status quo. (O—n).

F. 60 a TI. ♂ *b. 1916*

Retinochoroiditis. *1928*: Vision: R. E. and L. E.=Hand movements. Medias clear. Peripherally, masses of greyish-white foci and pigment. Patient difficult to examine; discs could not be seen. — Blindness stated to be noticed at 1 year of age, as in sister.

F. 60 b TI. ♀ *b. 1917*

Bilateral retinochoroiditis. *1930*: Vision: R. E. and L. E.=1/60. Suspected opacities of vitreous. Marked retinitic atrophy of discs, and peripherally possible abnormal coarseness of pigment. In the macular region on both sides a fairly large yellow-red focus. — *1955*: Vision: R. E. and L. E.=Perception of light. Pupils reacted to strong light. Visual fields could not be accurately tested, but she could judge the direction in which a light could be seen. No keratoconus. Discs sallow, of normal size. Vessels extremely narrow. Fundi: somewhat yellow-red and pale with a few black clumps of pigment in periphery. In macula, several black clumps of pigment, partly arranged in rings. (O—n). — *1955*: *ERG* of both eyes extinguished.

F. 61 a TI. ♀ *b. 1907, d. 1933 of pulmonary tuberculosis*

Bilateral retinochoroiditis. *1919*: Vision: R. E. and L. E.=Perception of light. No opacities of vitreous. Discs N. A. D. Peripherally, numerous large, yellow-white foci with relatively fine pigment.

F. 61 b TI. ♀ *b. 1911*

Bilateral retinochoroiditis. *1923*: Vision: R. E. and L. E.=0. Peripherally, both white and dark small foci. — *1946*: Completely blind. Small foci of pigment and pale spots over whole of both fundi. Constant, irregular eye movements made examination difficult. (L—n). — *1956*: Vision: R. E. and L. E.=0. Pupils did not react to light. Irregular eye movements. Corneas clear. Possibly, suggested keratoconus. Extensive cataract in posterior cortex of both lenses. Fundi: discs perhaps somewhat pale and vessels somewhat narrow. Maculas difficult to see, but presumably no marked changes at this site. In remainder of fundi, which were of normal colour, moderate number of evenly distributed, small black spots of pigment, usually irregularly triangular in shape. In a few places, large, irregularly shaped spots. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 62 a. ♂ *b. 1899, d. 1903 of renal disease*

Suffered from rickets. Severely retarded; unable to walk or talk. Stated to have been blind since birth.

F. 62 b TI. ♀ *b. 1906*

Bilateral retinochoroiditis. *1916*: Vision: R. E. and L. E.=0. — *1956*: Vision: R. E. and L. E.=0. Pupils did not react to light. Irregular eye movements. Marked keratoconus, no opacities. Right lens clear. In left lens, irregular but fairly dense posterior cortical cataract. Fundi: only peripheral parts of left fundus visible; they gave a red reflex, with a glimpse of some black pigmentations.

Owing to severe degree of keratoconus, right fundus also difficult to evaluate in detail. Normal red colour. Disc somewhat pale, vessels possibly somewhat narrow. No detailed evaluation of macula possible, but definitely no gross changes. In periphery, moderate number of small black pigmentations, mostly punctate or in form of streaks. (O—n). — *1956*: *ERG* not performed; the patient did not cooperate.

F. 63 a TI. ♀ b. 1916

Bilateral retinochoroiditis. *1928*: Vision: R. E.=0.1/60; L. E.=Hand movements. Pupils did not react to light. Medias clear. No pallor of discs; vessels somewhat narrow. Almost diffuse pigmentation round whole fundus. — *1946*: Only some perception of light and darkness on retinoscopy. Pupils did not react to light. Discs pale; vessels narrow. Scattered small pigmented foci over whole of both fundi. (L—n). — *1956*: Vision: R. E. and L. E.=Perception of light. Pupils reacted to light. Very slight nystagmus. Media of right eye: thin cataract in posterior cortex. Media of left eye: very fine posterior central cataract, and punctate central cataract in anterior cortex. Fundi: discs blurred and pale with narrow vessels. Macula of both eyes N. A. D. Remainder of fundi of normal colour, except for fairly numerous black pigmentations; some punctate, some in form of streaks and others of elongated triangular shape. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 63 b TI. ♀ b. 1918

Bilateral retinochoroiditis. *1930*: Vision: R. E. and L. E.=Hand movements. Dust-like opacities of the vitreous. In periphery, possibly a few pigmented foci. — *1931*: Vision: R. E. and L. E.=Perception of light. Dust-like opacities of the vitreous; in left eye a few larger opacities. Discs not definitely pale but retinal vessels somewhat narrow. Peripherally, large number of greyish foci with sparse pigmentation. — *1946*: Very faint perception of light. Pupils did not react to light. Discs pale, vessels narrow. Scattered, small foci of pigment over whole of both fundi. — *1956*: Vision: R. E. and L. E.=Perception of light. Pupils reacted to light. Moderate, slow nystagmus. Media clear. Corneas N. A. D. Fundi: no pallor of discs, but vessels somewhat narrow. The fundi had a markedly greyish colour, with lighter and darker patches. The maculas had the same colour. In periphery (not in macula) numerous black pigmented clumps, fairly large, irregularly rounded. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 63 c TI. ♂ b. 1920

Bilateral retinochoroiditis. *1930*: Vision: R. E. and L. E.=Hand movements. Numerous dust-like opacities of the vitreous. Retinitic atrophy with narrow vessels and numerous foci of pigment in periphery. — *1946*: Very faint perception of light. Pupils did not react to light. Discs pale, vessels narrow. Small foci of pigment scattered over whole of both fundi. (L—n). — *1956*: Vision: R. E. and L. E.=Perception of light. Right pupil did not react definitely to light, although the patient stated that he could sometimes distinguish light with this eye. Examination failed to disclose any light perception. Left pupil re-

acted faintly to light. Slow nystagmus. Divergent strabismus. Right eye: pale; fine aqueous flare, anterior synechiae. Discs blurred (signs of earlier iritis). Fundus could not be inspected. Left eye: media clear. Fundus: disc somewhat pale, vessels slightly narrow; reddish-yellow colour but no sharply defined pale atrophic foci. Fairly closely spaced black pigmenations, in the form of streaks or elongated triangles, over the whole fundus except in the macula. Here, the pigment was, however, slightly irregularly black-dotted. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 64 a (*65*) *TI.* ♂ *b. 1867, d. 1894*

Admitted to TI in 1897; no diagnosis or results of examination recorded. »Born blind.»

F. 65 a (*63*) *Lu.* ♂ *b. 1910, d. 1934*

Blindness observed at 7 months of age. Ophthalmologist then stated: »Retinal disease, incurable.» — Did not develop normally; severely retarded. Sent to »D—g S-s V—t» in 1916. Diagnosis: optic nerve atrophy? Transferred to Lund in 1923. Optic nerve atrophy. Vision: R. E. and L. E.=0. Since 1929, epileptic seizures and signs of endocrine dysfunction.

F. 65 b (*64*) *TI.* ♀ *b. 1917*

Bilateral retinochoroiditis. *1929*: Vision: R. E. and L. E.=0. Also diagnosed as »retinitis pigmentosa?». Plentiful branched pigment in fundi. Sparse, snuff-like opacities of the vitreous. No pallor of discs, arteries narrow. Maculas N. A. D. Plentiful, branched foci of pigment, and small pale foci peripherally in choroids. — *1956:* Vision: R. E. and L. E.=0. Pupils did not react to light. Marked keratoconus with a few small, central opacities in right cornea. Lenses clear except for a central opacity in posterior cortex of both eyes. Fundi: discs somewhat pale, vessels narrow. No changes in macular region. Elsewhere, numerous small and medium-sized black pigmented spots in the fundi and a few larger ones. The small ones were round or linear, and the larger ones in the form of streaks or elongated triangles. Below left disc, a large, pale atrophic area. (O—n). — *1956*: ERG of both eyes extinguished.

F. 66 a Tf. ♀ *b. 1906, d. 1944 of cerebral haemorrhage*

Bilateral retinochoroiditis. *1913*: Vision: R. E. and L. E.=0. Blindness observed at 3—4 months of age. No other notations. — Two of father's sibs born blind; nothing known about paternal grandfather's relations.

F. 67 a TI. ♀ *b. 1928*

Bilateral retinochoroiditis. *1935*: Vision: R. E.=0.6/60; L. E.=0.1/60. Medias clear. Discs and retinal vessels N. A. D. but punctate pigmentation peripherally. — *1945:* Vision unchanged. Arteries narrow. Discs somewhat sallow. — *1956*: Poor sight since birth, best in twilight, approximately unchanged throughout the years. Vision: R. E. and L. E.=Finger counting at 1 m. No limitation of visual fields (could be tested only with large objects or light). Distinct photophobia. No noteworthy eye movements. Pupils reacted to light. Marked bilateral

keratoconus with central opacities, largest in left eye. A few thin, spoked streaks of cataract in posterior cortex of both lenses. Fundi: ordinary colour; no marked changes except for some pallor of discs and slight narrowing of vessels. (O—n). — *1956*: *ERG* of both eyes extinguished? Strong blinking after light flash, but *ERG* probably extinguished.

F. 68 a V—ö. ♂ b. 1899, d. 1918 of pulmonary tuberculosis

No other data than »born blind, vision=0» and »congenital retinochoroiditis» noted for him on sister's ophthalmologic case record. Attended V—ö, but subsequently tuberculosis.

F. 68 b TI. ♀ b. 1909

Bilateral retinochoroiditis. *1921*: Vision: R. E. and L. E.=0. — *1946*: Constant, irregular eye movements which greatly impeded examination, but glimpses were seen of a few small black (round?) flecks of pigment scattered over the whole of both fundi. (A—m). — *1956*: Vision: R. E. and L. E.=0. Pupils did not react to light. Corneas clear. Marked keratoconus. Lenses clear. Synchysis scintillans in left eye. Fundi: discs possibly somewhat pale, vessels somewhat narrow. Small as well as slightly larger round spots of pigment over the greater part of the fundi. They were fairly far apart and were scarcely present in the macular region (this was somewhat hard to assess, owing to keratoconus and small size of pigmented spots). (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 69 a (70) TI. ♀ b. 1927

Bilateral retinochoroiditis. *1934*: Vision: R. E. and L. E.=0. Eyes strikingly small, somewhat sunken. Corneas of normal size. In left eye, peripheral radial opacities of the lens. Discs N. A. D. At any rate in lower part of left eye, scattered foci of pigment. — *1956*: Vision: R. E. and L. E.=Perception of light. Pupils reacted weakly to light. Sometimes nystagmus, sometimes irregular eye movements. Bilateral keratoconus, most conspicuous in left eye, in which there was also a central corneal opacity. Well-defined cataract peripherally and temporally in right lens; dense total cataract, somewhat shrunken, in left lens. Only right fundus could be seen; it had the usual colour. Here and there in periphery, black pigmented spots, chiefly small, fairly numerous at some sites. They were frequently in the form of streaks alongside the vessels. Those lying freely were most often small triangles or irregularly angular, but some round spots were also present. Only a few small dots were observed in the macular region. Discs somewhat pale, vessels slightly narrow. (O—n).

F. 69 b TI. ♂ b. 1932

Degeneration of the retina. *1939*: Vision: R. E. and L. E.=0. — *1946*: This patient was investigated at Tomteboda Institute in 1946 and selected as a proband. He left Tomteboda in the same year. Unfortunately, his record was mislaid in connexion with his discharge. Two attempts were made to reexamine him in the course of the field investigations, but he was not at home. Further attempts have been made to induce him to come to Karolinska Sjukhuset, but they have been unsuccessful.

F. 70 a (69) TI. ♂ b. 1888, d. 1917 of miliary tuberculosis

1900: Bilateral optic nerve atrophy. »Born blind.» No other notations.

F. 70 b (69). ♂ b. 1895, d. 1903.

Died shortly before reaching school age. »Born blind.»

F. 71 a TI. ♂ b. 1892

Bilateral congenital amblyopia. *1906*: Vision: R. E. and L. E. = Hand movements. No objective changes observed. — Blindness detected after scarlatina at 3 months of age. — *1955*: When he married in 1926, he could still count the lights in the Christmas tree. Could see whether or not electric light was turned on in room; now no longer possible. Vision: R. E. and L. E. = 0. Was stated to have previously seen only somewhat in the periphery, temporally, nasally and downwards; this vision gradually lost. Pupils did not react to light. Very slight cataract centrally in anterior and posterior cortex. Discs somewhat pale, otherwise of ordinary appearance. Vessels slightly narrow. Large and small pigmented spots scattered over whole of both fundi. The majority were round, but other shapes also occurred. Fundi had ordinary colour. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 72 a TI. ♂ b. 1914

Bilateral retinochoroiditis. *1928*: Vision: R. E. and L. E. = Perception of light. Pupils of medium width; rigid. Discs and central parts of fundi N. A. D. Peripherally, numerous, yellowish small foci with sparse pigment. — Blindness detected during first 6 months of life.

F. 73 a TI. ♀ b. 1927

Retinochoroiditis. *1937*: Vision: R. E. +5 = 0.1; L. E. +4 = 0.1. Medias clear. Pupils reacted to light. Yellowish (-reddish) discs with narrow arteries. Snuff-like pigment peripherally. Visual fields tested roughly: greatly limited upwards, somewhat downwards, little inwards and outwards. — *1944*: Vision: R. E. and L. E. = Jaeger 10 with difficulty, but both fairly good. — Impaired sight noticed already early in first year of life. — *1956*: Sight poor since birth, but worse with years. Could read as child, now impossible. Rapid, vertical nystagmus at times. Vision: R. E. and L. E. +7 = Finger counting at 0.5 m. Pupils reacted normally. Corneas N. A. D. Medias clear. Fundi: ordinary colour but perhaps some inricdence of yellow. Discs N. A. D. Arteries somewhat narrow. In periphery, fairly numerous small black foci of pigment and small pale punctate spots. Also medium-sized round black pigmented spots, and triangular as well as a few X-shaped, angularly elongated ones. Some accumulation of pigment along a few veins. Displacement of pigment in macular regions as well, but very inappreciable here and scarcely any in the foveal regions. (O—n). — *1956*: *ERG* of both eyes extinguished. *Flicker ERG* extinguished.

F. 73 b TI. ♀ b. 1929

Bilateral retinochoroiditis. *1937*: Vision: R. E. +7 = 2.5/50; L. E. +7 = 0.1. Visual fields (roughly tested) good. Pupils reacted to light. Medias clear.

Yellowish retinitic atrophy of discs. Vessels somewhat narrow. Maculas appeared to be fully normal. Increased pigmentation peripherally. — *1938*: Vision: R. E. +7=3/50 could not read Jaeger 10; L. E. +7=0.1 could read Jaeger 10 slowly. Discs markedly pale with narrow vessels. No pigmentary changes in macula, but no reflexes; fovea do. Peripherally, definitely pathologic pigment. — *1940*: Vision: R. E. + 7 ≤ 0.2 could scarcely read Jaeger 4; L. E.+7≤0.4 could read Jaeger 4. Visual fields for hand movements good. No marked pallor of discs, but changes peripherally in choroids in forms of countless yellowish foci. — Impaired sight stated in admission certificate to have been noticed at 2 years of age; patient therefore classified as secondary case. At follow-up examination, evident that sight had been impaired since birth. Physician sought at 2 years of age. Under constant control at Sahlgrenska Sjukhuset, Gothenburg, during whole childhood; diagnosis there heredodegenerative disease of retina. Attended ordinary local primary school for 1 year, but then sent to TI. — *1956*: Vision: R. E. +7=4/50; L. E. +7=0.1. Divergent strabismus of moderate degree. No noteworthy eye movements. Corneas N. A. D. Pupils reacted to light. Medias clear. Fundi: discs N. A. D. Arteries distinctly narrow and in some places of uneven caliber. Veins of ordinary width but some had considerable deposit of black pigment. Fundi of ordinary colour, possibly slightly yellow. Fairly plentiful small black pigmentations, alternating with yellowish-white small spots (pepper and salt appearance). At some places in periphery, not particularly dense accumulations of black pigment, of irregularly angular shape. Small, irregular displacements of pigment in macular regions, but none definitely present in foveal regions. Visual fields normal for white objects (1 cm^2). (O—n). — *1956*: *ERG* of both eyes extinguished. *Flicker ERG* suggested potentials at high light intensities. (G. Karpe).

F. 74 a TI. ♀ *b. 1927*

Bilateral congenital amblyopia. *1935*: Vision: R. E. and L. E.=Perception of light. No photophobia. Large, rigid pupils. No changes in medias or fundi. — *1939*: Vision: R. E. and L. E.=Perception of light. Inappreciable, incipient opacity of the lens temporally on both sides. Fundi N. A. D. Retinal dyscrasia?

F. 75 a. TI. ♂ *b. 1912*

Bilateral retinochoroiditis. *1919*: Vision: R. E. and L. E.=0. — *1956*: Vision: R. E. and L. E.=0. Irregular eye movements. Pupils did not react to light. Media of both eyes clear. Fundi: over whole of both fundi, except in macula, small, irregular black pigmented spots, fewer in periphery. They were not close together in any place. Discs somewhat greyish-pale and vessels somewhat narrow. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 76 a TI. ♂ *b. 1906*

Congenital retinochoroiditis of left eye and secondary cataract of right eye. *1914*: Vision: R. E. and L. E.=0. — Sum of marks 14 as compared to class median 13.2. — *1956*: Vision: R. E. and L. E.=0. Right eye: moderate keratoconus. Cornea clear. Dense cataract. Left eye: moderate keratoconus. Cornea

clear. In posterior lens capsule, a small well-defined cataract spot. Keratoconus considerably interfered with inspection of the fundus, but the disc could be seen to be somewhat pale, and vessels narrow. Centrally, a number of small pigmented spots; here and there in the periphery, larger ones. Colour fairly normal yellowish-red. View so poor that the state of the fovea could not be assessed. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 76 b TI. ♂ b. 1908

Complicated cataract (congenital retinochoroiditis?). *1916:* Vision: R. E. and L. E.=0. Blindness observed soon after birth. — Sum of marks 13.5 as compared to class median 12.7. — *1955*: Marked, severe keratoconus. Opacity of whole of both corneas; milky white in colour. (A—m).

F. 76 c Tf. ♀ b. 1910

Bilateral retinochoroiditis. *1917*: Vision: R. E. and L. E.=0. — *1923*: (Lund): Retinochoroiditis and bilateral optic nerve atrophy. — *1928*: Bilateral keratoconus and bilateral macula of the cornea. Medias otherwise clear. Dull atrophy of discs. Retina dull, with fine dusting of pigment. The whole of the fundus could not be seen, since the patient could not turn her eye to the left. — *1938*: Deep keratitis (degenerative?). — *1946*: Keratoconus, macula and degeneration of the corneas and bilateral retinochoroiditis (Lund). — *1917*: first trial at Tomteboda primary school. Discharged, but readmitted in 1918; spent one term there and was subsequently sent to Nynäshamn. Admitted to Lund in 1919 for special class instruction. The patient can be denoted as dull, but not as oligophrenic. It is interesting to note that the two youngest blind members of this family are each one of dizygotic twins, the other twin having normal sight.

F. 77 a TI. ♂ b. 1924

Congenital amblyopia. *1937*: Vision: R. E. and L. E.=0.1; had telescopic spectacles. Nystagmus. Otherwise, no objective changes. — *1938*: Vision: R. E. with glasses=0.1 could read Jaeger 10 poorly; L. E. with glasses=0.1 could not read Jaeger 10. — *1946*: Able to get about alone. Able to read newspaper with magnifying glass close to eyes, but not for any length of time. Medias clear. Fundi N. A. D. (L—n). — *1947* (Eye Department, L—g Hospital): Vision: R. E. +4.0=—3.0 180°=0.1; L. E.+2.5=Hand movements. Medias clear, discs oblique. — *1953* (Eye Department, L—g Hospital): Status quo.

F. 78 a TI. ♀ b. 1897, d. 1946 of cholecystitis

Bilateral retinochoroiditis. *1910*: Vision: R. E.=0.1; L. E.=5/60. Defective vision observed at 3 weeks of age, when a physician was consulted. — Could read large print, but not her own handwriting.

F. 79 a TI. ♂ b. 1903

Bilateral retinochoroiditis. *1916—24*: Vision: R. E. and L. E.=Perception of light. Retinal atrophy of discs. Reddish focus in both maculas. Peripherally, coarse branched pigments on an atrophic ground. — *1946*: Vision: R. E. and

L. E. = Perception of light; could distinguish between day and night. Numerous pigmentations, irregular and of varying size, over both fundi. Discs somewhat pale and vessels narrow. (L—n). — *1956*: Stated that he had just been able to get about alone as a small child. Sight deteriorated at about 30 years of age, so that he could only distinguish between light and darkness. Vision: R. E. and L. E. = Faint perception of light. Irregular eye movements. Pupils reacted to light, even if only very weakly. Media: both corneas N. A. D. Central, posterior cortical cataract in both lenses, denser in the right. Fundi: discs somewhat pale, vessels slightly narrow. Maculas seemed to be normal. The fundi were of ordinary colour, perhaps somewhat yellower. Numerous black pigmentations, both large and small; the majority were irregularly triangular and some resembled bone corpuscles. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 79 b TI. ♀ b. 1913

Bilateral retinochoroiditis. *1926*: Vision: R. E. = Hand movements; L. E. = Perception of light. Sparse opacities of the vitreous on both sides. Lenses clear. Discs and central parts of fundi N. A. D., but numerous, branched foci of pigment in periphery. — *1946*: Vision: R. E. and L. E. = Perception of light. Pupils reacted to light; both eyes similar. Numerous foci of pigment, irregularly shaped and of varying size, over both fundi. (L—n).

F. 80 a (81) TI. ♂ b. 1936

Amaurosis congenita. *1943*: Vision: R. E. and L. E. = 0. Incipient, superficial opacity in lower part of both corneas. A cloudy spoke in posterior cortex of both lenses. No marked pallor of the discs. No foci in fundi. — *1946*: No nystagmus but fairly marked irregular eye movements. Moderate number of opacities of vitreous. Margins of discs blurred, otherwise N. A. D. Vessels, macula and periphery of both eyes N. A. D. (O—n). — *1952*: Vision: R. E. and L. E. = 0. Fundi somewhat paler and markings coarser than normal. — *1956*: Had never seen light. Irregular eye movements. Vision: R. E. and L. E. = 0. Pupils did not react to light. Moderate keratoconus. Corneas clear. Thin streaks of cataract in spoke pattern in posterior cortex of both lenses. Fundi: no pallor of discs but vessels somewhat narrow. No other definite fundus changes; the reflex was the ordinary colour and no accumulations of pigment were present. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 81 a (80) TI. ♂ b. 1898

Retinochoroiditis. *1910*: Vision: R. E. and L. E. = Hand movements. — *1955*: Since childhood, had only seen light, never shapes. Subjectively, vision has remained unchanged. Inappreciable eye movements, moderate convergent strabismus. No fixation ability. Pupils reacted to strong light. Visual fields could not be estimated. Corneas clear. Inappreciable cataract in posterior cortex of both lenses. Fundi: discs somewhat pale with distinctly narrow vessels. Numerous medium-sized clumps of pigment, mostly round, over the greater part of he fundi; only the central parts fairly free from such pigmentation. (O—n). — *1955*: *ERG* of both eyes extinguished. — Superior intelligence, good social and financial position. Telephone-station supervisor.

F. 81 b (80) TI. ♂ b. 1901

Bilateral retinochoroiditis. *1912*: Vision: R. E. and L. E.=? poor. — Patient had always been greatly retarded; he had an abnormally large »rachitic» head and strikingly poor motor functions — »no control of his limbs». After an unsuccessful attempt at the primary school of TI, he was sent to the Asylum in Lund. There, signs of progressive cerebropathy appeared, with severe excitation and, in 1925—27, epileptic seizures. — *1946*: Diagnosis (Lund): optic nerve atrophy and bilateral retinochoroiditis.

F. 81 c (80) TI. ♀ b. 1905, d. 1925 of pulmonary tuberculosis

Bilateral retinochoroiditis. *1912*: Vision: R. E. and L. E.=Perception of light. Blind from birth, like her sibs. — *1922*: Status quo.

F. 82 a TI. ♀ b. 1937

Bilateral congenital amblyopia. *1944*: Vision: R. E.=Perception of light; L. E.=Hand movements temporally. Medias clear, discs and maculas N. A. D. — *1946*: No nystagmus but some irregular eye movements. Disc, vessels, macula and periphery of both eyes N. A. D. — *1953*: Vision: R. E.=Perception of light; L. E.=Hand movements temporally. Otherwise status quo.

F. 83 a TI. ♀ b. 1918

1926 (J—g Hospital): Congenital undulatory nystagmus, bilateral optic nerve atrophy and bilateral degeneration of retinal pigment. — *1931*: Bilateral retinochoroiditis. Vision: R. E. +1=2.5/60; L. E. +1=0.2, could not read Jaeger 10. Very small visual fields. Media and disc of both eyes N. A. D. In periphery, confluent, sparsely pigmented choratrophic foci. — *1938*: Vision: R. E.=3/50; L. E.=Perception of light. Visual fields small. Otherwise status quo. — *1946*: Completely blind. Pupils did not react to light. Considerable opacity of right lens. Left eye: large pale fields and smaller black pigmented foci scattered over whole fundus. Disc seemed to be normal. (L—n). — Epileptic seizures since 1934; infrequent, usually in connexion with menstruation. Controlled by medication.

F. 84 a TI. ♂ b. 1910

Bilateral retinochoroiditis. *1922*: Vision: R. E. and L. E.=0. Central parts N. A. D. Inappreciable changes in periphery. In right lens, an opaque spoke temporally. — *1946*: Completely blind. Pupils did not definitely react to light. Bilateral keratoconus. Cataract in left eye. Difficult to examine, owing to constant, rolling eye movements, but no marked changes could be observed. (A—m). — *1956:* Blind from birth. Vision: R. E. and L. E.=0. Pupils did not react to light. Irregular eye movements. Marked keratoconus with central opacities. Fairly dense cataract in lower part of left lens, extending posteriorly towards the centre. Right lens clear. Fundi: discs somewhat pale, vessels somewhat narrow. No changes seemed to be present in either macula. The fundi had the ordinary red reflex. A small number of black pigmented spots present in the periphery; they were small and irregularly rounded. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 85 a (50) TI. ♂ b. 1900

Bilateral optic nerve atrophy. *1915*: Vision: R. E. and L. E.=0. In both eyes, artefact aphakia with clear gaps in the after-cataract. Pale discs with blurred margins. — *1946*: Vision: R. E. and L. E.=0. Eyes deeply sunken and small, fixed in turned-up position. Could not turn his eyes downwards to permit inspection. (L—n). — Blindness observed at 5 months of age, when he was severely ill with headache and convulsions. This was regarded as the cause of blindness. Development subsequently retarded; did not walk until 5 years. Some intellectual inferiority, but managed primary school at Växjö and 4 classes at TI, where the requirements were very high. — *1908*: Operation for bilateral cataract (before starting school). — It is reasonable to assume, according to medical certificate of 1909, that blindness was congenital and independent of meningitis. — *Cf.* brother 85 b.

F. 85 b (50) TI. ♂ b. 1908

Retinochoroiditis left eye and complicated cataract right eye. *1919*: Vision: R. E.=0; L. E.=Perception of light. Total cataract in right eye. Several opaque spokes in posterior cortex of left lens. Fundus: numerous yellow-white small foci in the periphery, with extremely sparse pigmentation. No apparent changes in central parts. — *1956*: Right eye enucleated owing to rise in tension. Vision: R. E.=Prothesis; L. E.=0. Pupil did not react to light. Irregular movements of left eye. Marked keratoconus of left eye, with small cataract opacities in cornea. Wedge-shaped cataract in posterior cortex of lens. Fundus: disc somewhat pale, vessels narrow. The macula could not be judged in detail, but did not seem to exhibit any marked changes. The fundus had the ordinary colour. Moderate amount of black pigment in the periphery, mainly in the form of small and somewhat larger spots, but occasional streaks. (O—n). — *1956*: *ERG* of left eye extinguished (right eye: prothesis).

F. 86 a TI. ♂ b. 1935

Amaurosis congenita. *1943*: Vision: R. E. and L. E.=0. No objective fundus changes. — *1945*: Bilateral keratoconus; clouding in right apex, left clear. — *1946*: Bilateral retinochoroiditis. No nystagmus but considerable irregular eye movements. Keratoconus with central opacity in right eye. Discs and vessels N. A. D. Macula itself not definitely altered but in its vicinity, as well as in the periphery, the pigment was in some places clumped into fairly large black dots. These alternated with white round atrophies of varying size (from smallest size to $^1/_8$ disc-size). At some sites, the changes were of disseminated choroiditis type. Right eye and left eye similar. (O—n). — *1953:* Status quo. — Neurologically and mentally N. A. D. Highly intelligent. Lower certificate exam. (Realexamen) 1952, thereafter further studies.

F. 86 b Lu. ♂ b. 1939

Admitted to Tomteboda home for blind children in 1941. Transferred to Lund 1948. — Like brother, examined in home on field investigation in 1946: small and thin for his age, pale. Mentally deficient to imbecile, I. Q. 47. Choreatic twitchings. Eyes: small sunken eyeballs, bilateral keratoconus. Fundi

could not be inspected. Completely blind. (A—m). — Additional diagnosis in Lund 1948: Bilateral optic nerve atrophy.

F. 87 a TI. ♀ *b. 1913*

Bilateral retinochoroiditis. *1923*: Vision: R. E. and L. E.=Perception of light. Slight peripheral opacity of the lens. Numerous yellow-white spots and branched pigment. — *1931:* Status quo. — *1956:* Vision: R. E. and L. E.=0. Pupils did not react to light. Moderate irregular nystagmus. Cornea of both eyes clear. No keratoconus. Bilateral, central cataract in anterior and posterior cortex; it did not prevent inspection to any great extent. Fundi: numerous large clumps of black pigment, somewhat less in extreme periphery. The maculas contained no such pigmentations. The fundus colour was reddish-grey, in some places between the pigmented spots it was yellowish-grey. Discs greyish; vessels narrow. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 87 b TI. ♂ *b. 1917*

Bilateral retinochoroiditis. *1931*: Vision: R. E. and L. E.=Perception of light. Medias clear. Numerous foci of pigment, some branched, over the whole of both fundi, except centrally. — Blindness observed at about 1 month of age. — *1926*: Vision: R. E. and L. E. $<$ 1/60. — *1956*: Defective vision since birth, but could see large objects as a small child. Now only able to distinguish light from darkness. Vision: L. E. and R. E.=Perception of light. Pupils reacted to light. Slow nystagmus and irregular eye movements. Corneas N. A. D. Small punctate cataract in anterior cortex of both lenses and moderately dense, extensive cataract in posterior cortex. Despite these, parts of the fundi could be seen fairly well. Reflex yellowish-red. Discs somewhat pale, vessels slightly narrow. Numerous black pigmented spots, both round small ones and irregularly angular small and somewhat larger ones. Macular regions seemed to be largely free from such pigmentations. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 87 c TI. ♀ *b. 1920*

Bilateral retinochoroiditis. *1932*: Vision: R. E. and L. E.=Perception of light. Wide, reactionless pupils. Discs somewhat pale and vessels narrow. Numerous, partly branched foci of pigment as in retinitis pigmentosa. — *1956*: Vision: R. E. and L. E.=Perception of light. Pupils reacted very faintly to light. Irregular, lively eye movements. Corneas N. A. D. Round cataract in anterior cortex of both lenses. Fundi somewhat pale red. Discs slightly pale, vessels round. Numerous black pigmented spots, both punctate and in streaks, many in shape of elongated triangle. Only a few spots of pigment in macular regions. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 88 a TI. ♀ *b. 1937*

Bilateral retinochoroiditis. *1944*: Vision: R. E. and L. E.=Perception of light. Pupils reacted, although weakly, to light. Cataract in right eye. Media of left eye clear. Fundi: marked displacement of pigment, chiefly in periphery. Alternating black dots and network of atrophic areas. Tonus normal. — *1946*:

Bilateral keratoconus. Corneas clear. Dense cataract in right eye. Media of left eye clear. Disc somewhat blurred. Vessels fairly narrow. Macula N. A. D. In periphery, numerous yellowish spots, alternating with clumps of pigment. (O—n). — *1953*: Marked keratoconus. Vision: R. E. and L. E.= Perception of light.

F. 89 a TI. ♀ *b. 1933*

Bilateral congenital amblyopia. *1941*: Vision: R. E. = Hand movements; L. E.=1.5/60. Considerable nystagmus. Large, possibly total excavations. No pallor of discs. Tonus felt approximately normal. — *1943*: Vision: R. E.=Hand movements; L. E.=1/25. Reads with magnifying glass but not Jaeger 10. — *1945*: Vision: R. E.=Hand movements; L. E.=1—2/50. No improvement with glasses. Pupils reacted very weakly to light, the left better. Fundi, clumping of pigment. Discs somewhat greyish, not pale. — *1946*: Discs irregularly shaped with small temporal conus; no pallor. Vessels normal. Maculas and periphery N. A. D. — *ERG* unsuccessful on account of constant eye movements. — *1948—51*: Status quo. (O—n).

F. 90 a. ♀ *b. 1914, d. 1918*

»Blindness observed soon after birth», as in brother. Seems to have perceived hand movements in front of her eyes but not objects held out. Could walk only with the help of a go-cart; could not feed herself. Talked intelligibly but had difficulty in understanding. Was considered to be mentally retarded. Died of »a stroke» at $4\,^{3}/_{4}$ years of age.

F. 90 b TI. ♂ *b. 1917*

Retinochoroiditis. *1929*: Vision: R. E.=3/60; L. E.=4/60. Marked nystagmus. Pupils did not react distinctly to light. Medias N. A. D. Discs somewhat pale with greatly constricted arteries. Far out in periphery, numerous small pale foci with only occasional flecks of pigment. — *1936*: Vision: R. E.=2/60; L. E.=3/60. Hemeralopia. Visual fields minimal. — *1946* (Eye Department, Lund Hospital): Bilateral congenital amblyopia (and atrophic retinopathy?). Just able to get about alone and had learnt to read large type. Vision: R. E. and L. E.=Perception of light. Hand movements at 1 m. Tension: R. E. 22; L. E. 24. Marked undulatory nystagmus, particularly on fixation (in attempt to test visual acuity). Medias clear. Pupils reacted to light. Difficult to evaluate ophthalmologically, on account of nystagmus. Both discs pale and vessels narrow. Fundi as a whole faintly pigmented.

F. 91 a TI. ♀ *b. 1937, d. 1950 of meningitis*

Bilateral optic nerve atrophy. *1944*: Vision: R. E. and L. E.=0. — *1946—50*: No nystagmus. Vision: R. E. and L. E.=0. Pupils did not react to light. Fundi: discs extremely pale, arteries somewhat narrow. Macula and periphery of both eyes N. A. D. (O—n).

F. 91 b TI. ♂ *b. 1941*

Congenital amblyopia. *1949*: Vision: R. E. and L. E.=Perception and localization of light. Medias clear. Discs moderately to inappreciably pale, vessels

somewhat narrow. Otherwise N. A. D. No nystagmus. (O—n). — *1951—55*: Status quo. (O—n). — *1956*: Incipient keratoconus. Otherwise status quo. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 92 a TI. ♀ *b. 1934*

Bilateral congenital amblyopia. *1945*: Vision: R. E. and L. E. = 2/50. No improvement with glasses. Nystagmus. Medias N. A. D. Disc, macula and periphery of both eyes seemed to be normal. — *1946:* Slow nystagmus. Discs somewhat pale with narrow arteries. Macula and periphery of both eyes N. A. D. (O—n). — *1953*: Status quo. (O—n).

F. 92 b TI. ♀ *b. 1936*

Bilateral congenital amblyopia. *1945*: Vision: R. E. = 1.5/60; L. E. = 1.1/60. Media, disc, macula and fundus of both eyes N. A. D. — *1946*: Slow nystagmus. Discs, vessels and periphery N. A. D. Centrally in the macula of both eyes, a small round, sharply defined reddish-yellow atrophic focus. (O—n). — *1949*: Vision: R. E. and L. E. = 2/50. No improvement with glasses. — *1953*: status quo. (O—n).

F. 93 a V—ö. ♀ *b. 1921, d. 1930*

Facial erysipelas twice in 1929—30; admitted to local hospital: »Blind since birth. Despite blindness, well developed mentally. Pupils did not react to light.» No other record of ophthalmologic condition. — After first attack of erysipelas, proteinuria persisted and the patient died of uraemia.

F. 93 b TI. ♂ *b. 1922*

Bilateral congenital amblyopia. *1933*: Vision: R. E. and L. E. = Perception of light. Keratoconus? Radial small opacities in posterior lens cortex. Colour of discs not markedly changed but vessels appeared somewhat narrow. Snuff-like pigment (pathologic?) peripherally. — *1938*: Bilateral degeneration of the retina. Several clouded spokes. Strikingly few objective changes, except for yellowish colour of discs and a little coarse pigment peripherally. — *1956*: Vision: R. E. and L. E. = Perception of light. Pupils reacted to light although weakly. Irregular eye movements. Cornea of both eyes N. A. D. Both lenses clear, except for one small cataract spoke in each lens. Fundi: ordinary colour and appearance. No atrophy or pigmentary displacement visible. No marked pallor of discs. Possibly some narrowing of vessels. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 94 a Kr. ♂ *b. 1884*

This patient is stated to have seen best of all four sibs with impaired vision in this family. He struggled through ordinary elementary school with the teachers' help. Always had to sit by a window, »darkness in the schoolroom». Could not see blackboard from his place, had to go right up to it. Allowed to have larger handwriting than the other children. Good at arithmetic. Could read newspapers and books if held close to his eyes. After 14—15 years of age, this became increasingly difficult. Could glimpse contours of approaching per-

sons, *e. g.* distinguished between adults and children. Unable to se details, recognized people by their voice. Admitted to Kristinehamn vocational training school for blind at 29 years old; learnt braille there. Patient stated that his vision remained stationary in youth. Deteriorated after about 40 years old, when he was no longer able to get about alone. *1956*: For about past 10 years no sight in his left eye, for about past 5 years none in his right. Vision: R. E. and L. E. = 0. Irregular eye movements. Corneas clear. In both lenses, posterior cortical cataracts; dense centrally and thinner peripherally. Fundi could nevertheless be seen fairly well. Discs somewhat pale, vessels narrow. Fundi had yellowish-red colour and were strewn with round, confluent black spots of pigment. Sparser in maculas, but here the conditions were hard to judge on account of cataract. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 94 b V—ö. ♀ b. 1887

Stated that all the blind sibs had had impaired sight since birth, with subsequent deterioration. Course approximately the same in all of them. The patient struggled through the first 2 classes in the local elementary school. Could only read large type and only for a short while. The teacher considered that she did not try hard enough. At the end of a term, »the rector of the parish raised an alarm» and arranged for admission to Växjö school for the blind; the parents did not know about its existence. — As a child, could distinguish people but not details, *e. g.* their features. After scarlatina at 17 years old, her sight became much worse; like a veil over the whole visual field. Had never had tube vision or anything that could be interpreted as such. Both the patient and her affected sibs were practically helpless after dark. — *1955*: Vision: R. E. = 0; L. E. = Perception of light. No improvement with glasses. Right pupil did not react definitely to light, left weakly. Corneas clear. Bilateral cataract fairly inappreciable in size, most in posterior cortex. Discs somewhat pale, vessels slightly narrow. Fundi: plentiful black clumped pigment peripherally, some lying alongside the vessels. Macular regions practically free from such pigmentation. Picture not that of retinitis pigmentosa. (O—n).

F. 94 c TI. ♀ b. 1894, d. 1926 of pulmonary tuberculosis

Bilateral optic nerve atrophy. *1905*: Vision: R. E. = 1.5/60; L. E. = 2/60.

F. 94 d TI. ♂ b. 1900

Bilateral retinochoroiditis. *1912*: Vision: R. E. = 4—5/60; L. E. = 1.5/60. Marked hemeralopia. Snuff-like pigment over fundi. Diagnosis in Växjö (1907) bilateral optic nerve atrophy. — *1956*: Vision: R. E. = Hand movements against very light background; L. E. = 0. Right pupil reacted to light although weakly, left did not react. No noteworthy eye movements. Corneas N. A. D. Medias clear. Fundi: numerous black spots of pigment of varying size, chiefly round, some confluent. Also a few very large, irregularly shaped grey pigmented spots. In macular regions only sparse pigmentations, mostly small, but the colour as in fundi otherwise atrophic greyish. Discs palely grey, arteries extremely narrow. (O—n).

F. 95 a Lu. ♀ *b. 1920*

Highly mentally retarded; had never learnt to walk or talk properly. Admitted to Asylum in Lund. — *1931* (Lund): Cataract and optic nerve atrophy. External parts of eye N. A. D. Pupils did not react to light, but they made slow movements as in changes in accomodation. Bilateral incipient cataract, most advanced in left eye. Discs pale with sharp, irregular margins. Vessels extremely narrow, could not be traced for more than about a disc's diameter from the discs. Fundi: faintly brown pigmented in periphery. — *1946*: On the whole, status quo. Difficult to examine. (Lund).

F. 95 b TI. ♂ *b. 1935*

Bilateral hereditary degeneration of the retina. *1942*: Vision: R. E. and L. E.=0. Pupils rigid. Medias N. A. D. No changes in discs, but in periphery large number of pale, yellowish foci and fine dashes of pigment. — *1946*: No nystagmus but some irregular eye movements. Discs and vessels N. A. D. Maculas normal. In periphery of both fundi, numerous depigmented spots of yellow-red colour and a number of clumps of pigment, both linear and dotted; not of the pepper and salt type. (O—n). — *1951*: Status quo. (O—n).

F. 96 a TI. ♀ *b. 1932*

Bilateral retinochoroiditis. *1939*: Vision: R. E. and L. E.=Perception of light. Fundi: numerous greyish foci and dashes of pigment, particularly in periphery. No evident disc changes. — *1946*: No nystagmus. Discs moderately pale, not yellowish; vessels slightly narrow. In macula, an oval disc-sized are of atrophy with a light-red peripheral zone and a central dark, brownish spot. Halfway peripherally, numerous small black pigmented spots of irregular shape; some in shape of bone corpuscles. Peripherally, yellowish atrophic small spots. Pupils reacted uncertainly to light. (O—n). — *1949*: Status quo. Pupils reacted distinctly to light. (O—n).

F. 97 a TI. ♀ *b. 1898, d. 1923 of chronic nephritis*

Bilateral retinochoroiditis. *1909*: Vision: R. E. and L. E.=0. — *1914—23* (Vänersborg and Lund): Bilateral macula of the cornea and optic nerve atrophy? Nystagmus. — Since 1916, schizophrenic psychosis. Had mediocre marks in primary school and marked difficulties in elementary school.

F. 98 a TI. ♀ *b. 1892, d. 1934 of pulmonary turberculosis*

Bilateral retinochoroiditis. *1907*: Vision: R. E. and L. E.=0.2/60. Very faintly marked, small pale foci strewn over whole of both fundi. Slight retinitic atrophy. — *1934* (Sanatorium): Could glimpse a flame of light in the room but not able to go about alone. Discs somewhat pale and margins slightly blurred. Vessels narrow, particularly in right eye. Retina atrophic. Fundi: as a whole, streaked and spotted with diffusely scattered black pigmentations.

F. 99 a TI. ♀ *b. 1930*

Bilateral congenital amblyopia. *1940:* Vision: R. E. +1.5 95°=4/50; L. E. ± ±0=4/50. Marked nystagmus. Pupils reacted to light. No objective changes. —

1946: Vision: R. E. and L. E. ±0=0.1. Disc, vessels, macula and periphery of both eyes N. A. D. — *1948*: Status quo. *ERG* unsuccessful owing to nystagmus.

F. 100 a TI. ♀ *b. 1912*

Bilateral congenital amblyopia. *1924*: Vision: R. E.=1/60; L. E.=0.7/60. Pupils more than medium width; did not react to light. Marked nystagmus. Medias and fundi N. A. D. No photophobia. Colour-blind for red and green. — *1932*: Bilateral retinochoroiditis. Vision: R. E. and L. E.=1.5/60. Still greater limitation of visual fields. Discs not pale, but had a yellowish tinge. Vessels distincly narrowed, more on left side. Fundi: peripherally, coarse, granular pigment and a few small pale foci. — Blindness was detected soon after birth, as in the patient's brother. Both considered that they had seen »somewhat better formerly». It should, however, be noted that the visual acuity remained practically stationary for almost 30 years. The patient struggled through the local primary school, although both the physician and authorities urged sending her to TI. Parents refused and were supported by teacher. Not until after death of both parents were the two sibs sent to TI. — *1955*: Vision: R. E. and L. E.=1/50. Sometimes nystagmus, often irregular eye movements. Visual fields appeared good. Pupils reacted well to light. Discs somewhat pale, not blurred, with sharp margins. Vessels extremely narrow Fundi: ordinary colour. In a few places in the periphery, small sharply-defined circular pigmentations. Otherwise nothing noteworthy. (O—n). *1955*: *ERG* of both eyes extinguished.

F. 100 b TI. ♂ *b. 1917*

Bilateral congenital amblyopia. *1928*: Vision: R. E. = 1.5/60; L. E. = 1/60. Pupils rigid. No changes in either media or fundus. Bilateral retinitic atrophy of the discs? — *1932*: Anterior retinochoroiditis? Vision: R. E. and L. E.=2/60. Moderate narrowing of retinal vessels; discs slightly yellow-tinged, otherwise N. A. D. Fairly large visual fields. — *1939—42*: Status quo. — »Finger counting at 1 m» noted in 1924. — The patient has for several years been employed as a masseur at the Public Baths and does well financially. — *1955*: Vision: R. E. and L. E.=1/50. Sometimes nystagmus, sometimes irregular eye movements. Pupils reacted well to light. No limitation of visual fields temporally, but limitation nasally. Hand movements or light perceived only at about 10° nasally. Discs somewhat pale, not blurred, with sharp margins. Vessels definitely narrow, but not as narrow as in his sister 100 a. Fundi: ordinary colour. No spots of pigment visible nor anything else noteworthy. (O—n). — *1955*: *ERG* of both eyes extinguished.

F. 101 a (52) TI. ♂ *b. 1930*

Bilateral congenital amblyopia. *1938*: Vision: R. E. and L. E.=Hand movements. Nystagmus. Pupils did not definitely react to light. No photophobia. No evident fundus changes, except somewhat suspected such downwards in the periphery. — *1944*: Vision: R. E. and L. E.=Hand movements. Suggested keratoconus. A few corneal opacities, chiefly in the left eye. Somewhat difficult to examine owing to nystagmus, but fundi apparently normal. — *1946:* Moderate nystagmus, but at times lacking. Pupils reacted distinctly to light. Cen-

tral, fairly dense corneal opacity in left eye. A few opacities of the vitreous, one of them round, dense and well-defined in right eye. Disc, vessels, macula and periphery of right eye N. A. D. Left eye on the whole similar to right, except for clumping of pigment in macula. (O—n). — *1948:* Keratoconus with central opacities on both sides. Otherwise status quo. (O—n).

F. 102 a TI. ♀ b. 1909

Bilateral retinochoroiditis. *1921*: Vision: R. E. and L. E. = Perception of light. — *1956*: Vision had always been about the same as now; able to distinguish between light and darkness. Vision: R. E. and L. E. = No demonstrable perception of light. Pupils did not react to light. Irregular eye movements. Marked keratoconus with small central opacities. Bilateral anterior and posterior cortical cataracts, the former round and central, the latter wedge-shaped in outline. Fundi only partly visible; discs pale but not white. Vessels narrow. In periphery, moderate number of black pigmented spots, mostly round. Neither macula could be definitely evaluated, but no changes seemed to be present. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 102 b TI. ♀ b. 1912

Bilateral congenital retinochoroiditis. *1923*: Vision: R. E. and L. E. = Hand movements. Radial opacities of the lens. Branched pigment peripherally. — *1956*: Vision poor since birth, some deterioration with age. Vision: *R. E.* = Perception of light; L. E. = Uncertain perception of light. Right pupil reacted slightly to light, the left not at all. Irregular eye movements. Moderate keratoconus. Both corneas clear. Fine precipitate on Descemet's membrane in left eye; fine aqueous flare. Dense, diffuse cataract in this eye (all indicating slightly active chronic uveitis). In right eye, a round small paracentral cataract opacity in posterior cortex. Media otherwise clear. Left fundus not visible. Right fundus: disc somewhat pale and vessels slightly narrow. No apparent change in macula. Ordinary red reflex in fundus, but fairly numerous medium-sized black pigmented spots, mostly irregular in shape, in periphery. Some smaller round spots also present. (O—n). — *1956*: *ERG* of both eyes extinguished.

F. 102 c V—ö, Lu. ♀ b. 1915

1926 (Lund): Retinochoroiditis and bilateral optic nerve atrophy. Vision: R. E. and L. E. = 0. — *1946* (Lund): Bilateral disseminated retinochoroiditis and bilateral optic nerve atrophy. — *1948* (Lund): Glimpses light and darkness? — Signs of mental disease with some lability of affect appeared in 1926. The patient was therefore sent to the asylum in Lund after attending the primary school at TI, instead of proceeding to the elementary school. Mental disease with katatonic phases of uneasiness, with intermittent improvement, developed there. Stereotyped movements and catalepsy started in 1941. — Early schizophrenia of katatonic type.

F. 103 a TI. ♀ b. 1904

Retinochoroiditis. *1917*: Vision: R. E. and L. E. = Perception of light. Coarsely branched pigment in fundi. — *1946*: Could distinguish between light and dark-

ness. Pupils reacted to light. Marked keratoconus of left eye, less of right. Bilateral cataract entirely obscuring. (L—n). — *1956*: Greatly impaired vision since birth, only distinguished light from darkness; still poorer with time. Vision: R. E. and L. E.=Uncertain perception of light. Pupils did not react markedly to light. Advanced keratoconus with large central corneal opacities. In the lens, the cataract was seen to fill the whole region of the pupils; the right was greyish-white, the left yellowish-white, very dense. The fundi could not be seen. The general appearance of the eyeballs was somewhat atrophic. (O—n). — *1956*: *ERG* of right eye extinguished; that of left eye was impossible to record.

F. 104 a Tf. ♀ *b. 1938*

Amaurosis congenita. *1945*: Vision: R. E. and L. E.=0. Medias clear. No pallor of discs; margins somewhat blurred. Pigment slightly uneven, not definitely pathologic. — *1946*: Irregular eye movements. Discs somewhat pale with extremely narrow vessels. Macula and periphery of both eyes N. A. D. (O—n). — *1953*: Keratoconus. (O—n).

F. 105 a Tl. ♂ *b. 1906*

Retinochoroiditis. *1913*: Vision: R. E. and L. E.=0. »Complete blindness» detected at 3 months of age. — *1956*: Vision: R. E. and L. E.=Very faint perception of light. Most certain reaction was obtained by illuminating the fundi in darkness with a strong light. Pupils reacted very weakly to light. Some irregular eye movements at times. No nystagmus. Distinct keratoconus with small central opacities in left eye. Right cornea N. A. D. Lens of both eyes clear. The fundi had the ordinary colour. No definite changes in either macula. In periphery, moderate number of small pigmented spots, both punctate and round, as well as irregularly triangular and linear. Discs somewhat pale, vessels narrow. (O—n).

F. 105 b Tl. ♀ *b. 1911*

Bilateral retinochoroiditis. *1923*: Vision: R. E. and L. E.=Hand movements. »Born blind.» — *1928* (Lund): Bilateral retinochoroiditis. Vision: R. E. and L. E.=Perception of light. Discs pale, vessels narrow. Choroidal foci strewn over fundi, and pigmentations of the pepper and salt type peripherally. — *1956*: Impaired vision since birth, no noteworthy change. Vision: R. E. and L. E.=Perception of light. Pupils reacted to light, although weakly. Irregular eye movements. Cornea and lens of both eyes N. A. D. Fundi: scarcely any pallor of discs, but markings somewhat blurred. Vessels slightly narrow. The fundi had the ordinary red colour. In periphery, numerous fairly small black spots of pigment, most of them irregularly angular. No such pigmentations nor any other visible changes in the macular regions. (O—n). — *1956*: *ERG* of both eyes extinguished.

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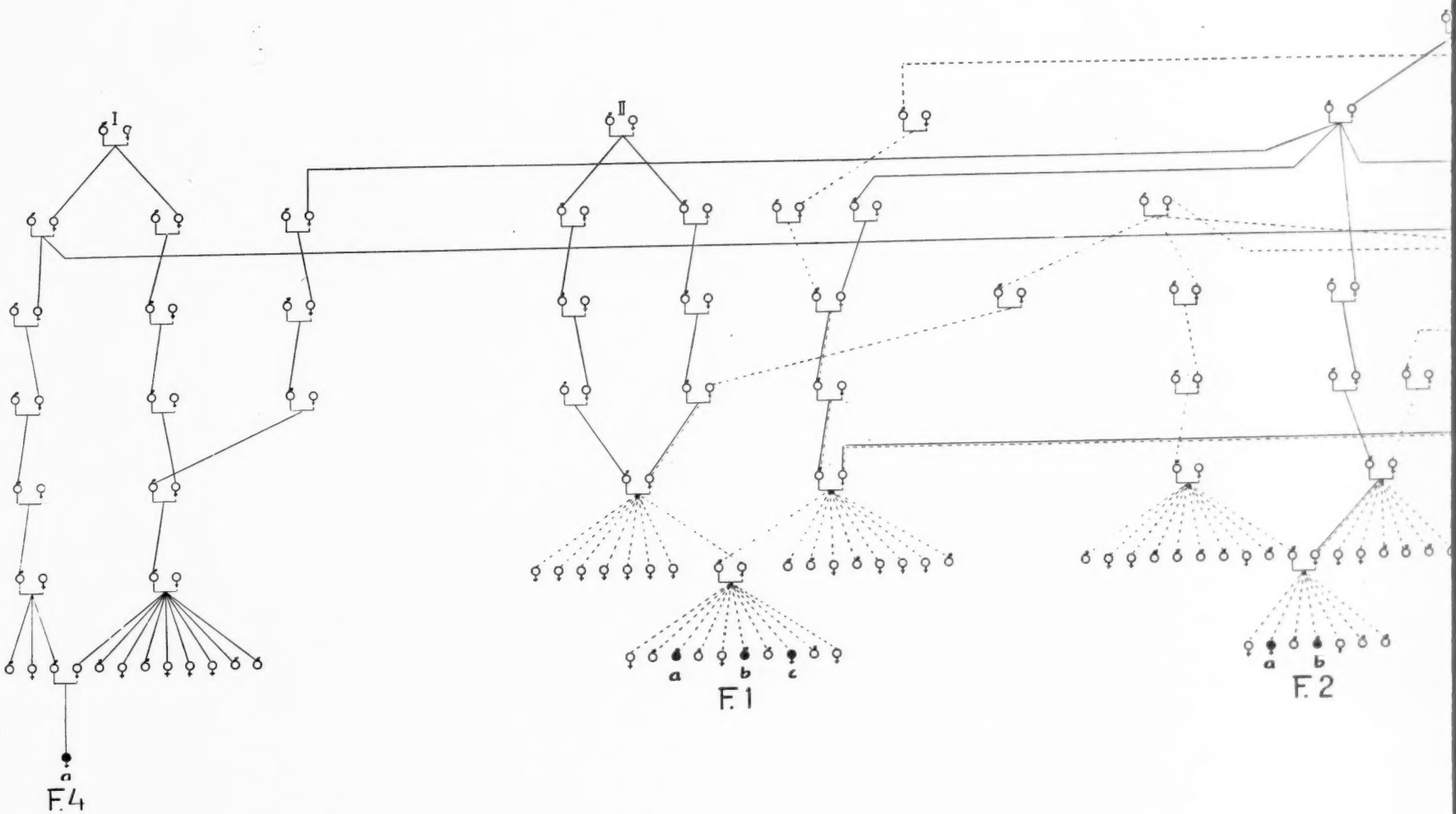
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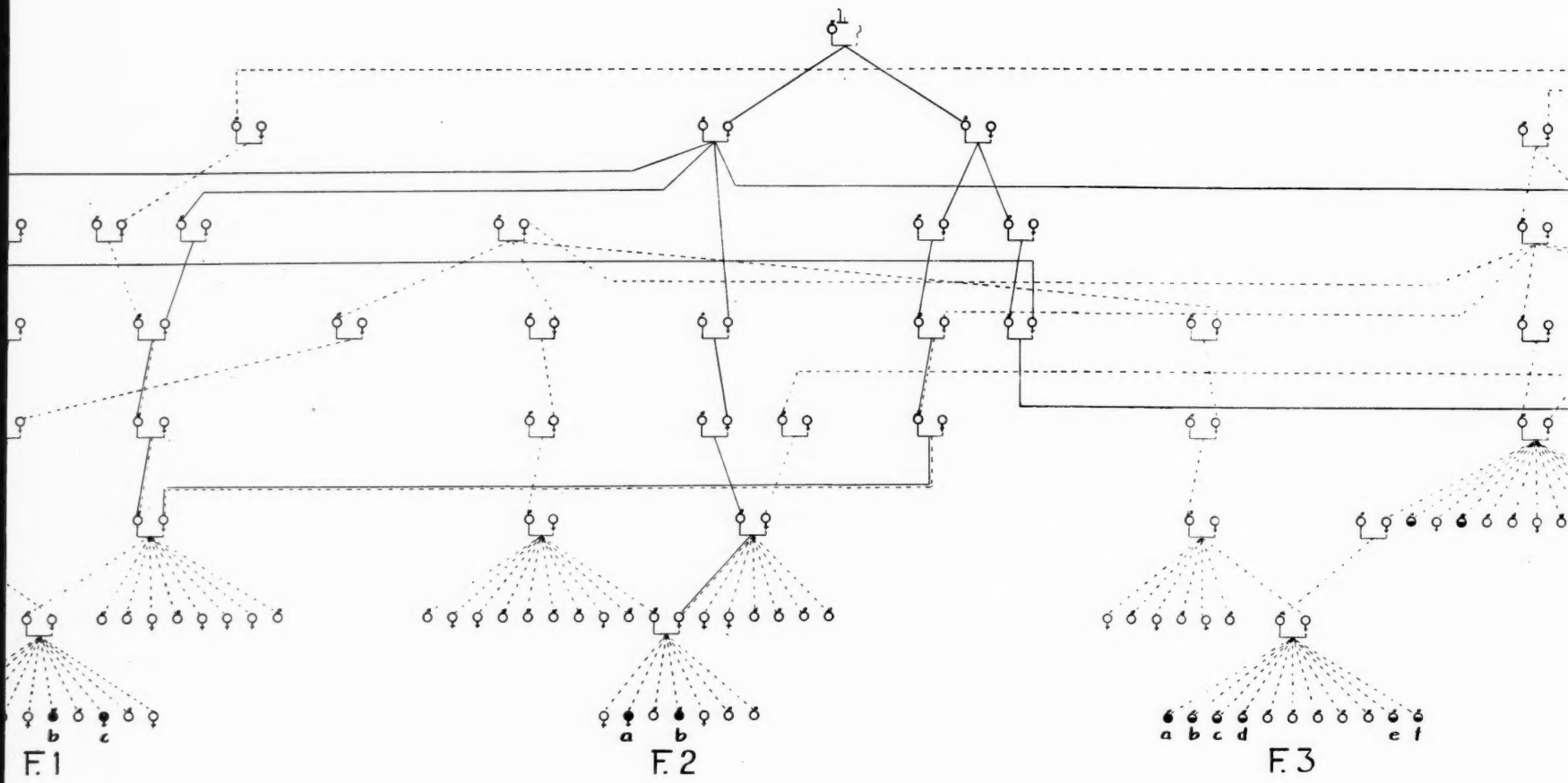

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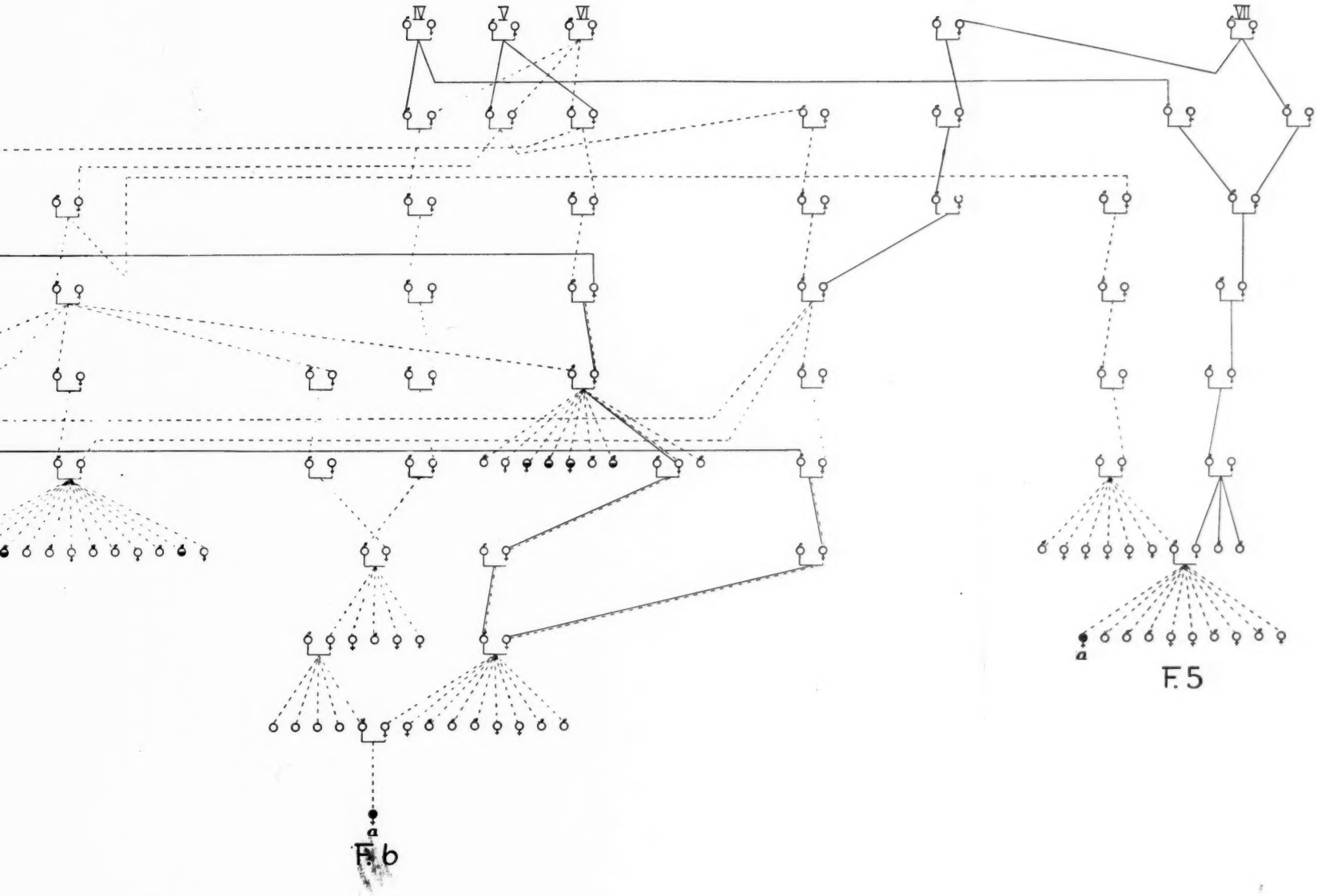
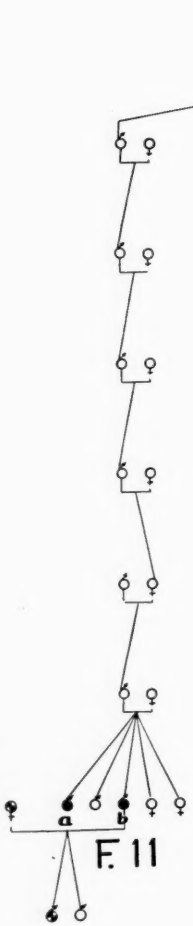


F. 5

F. b



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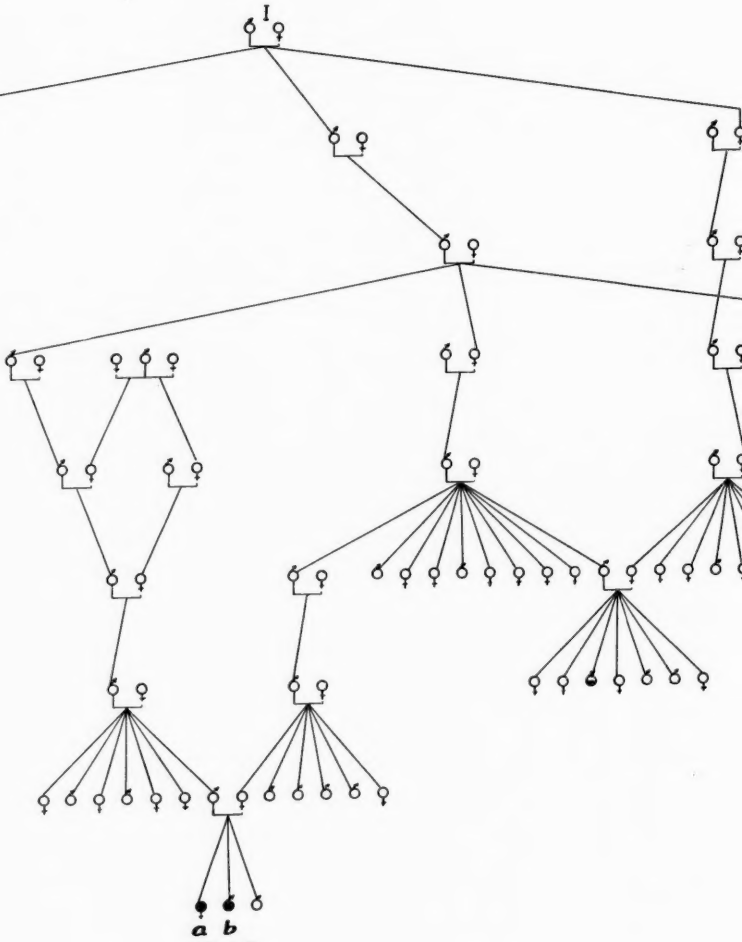

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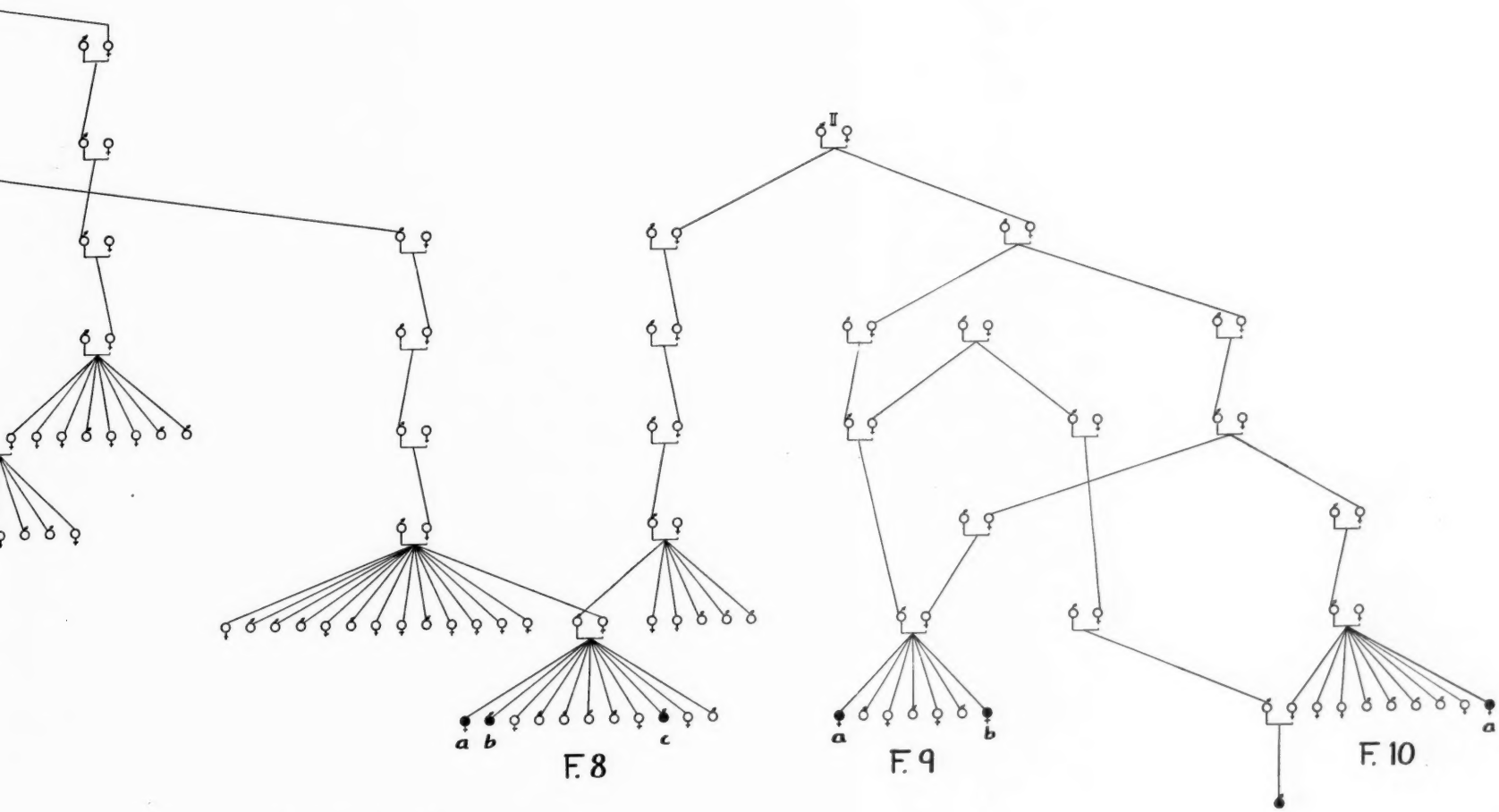

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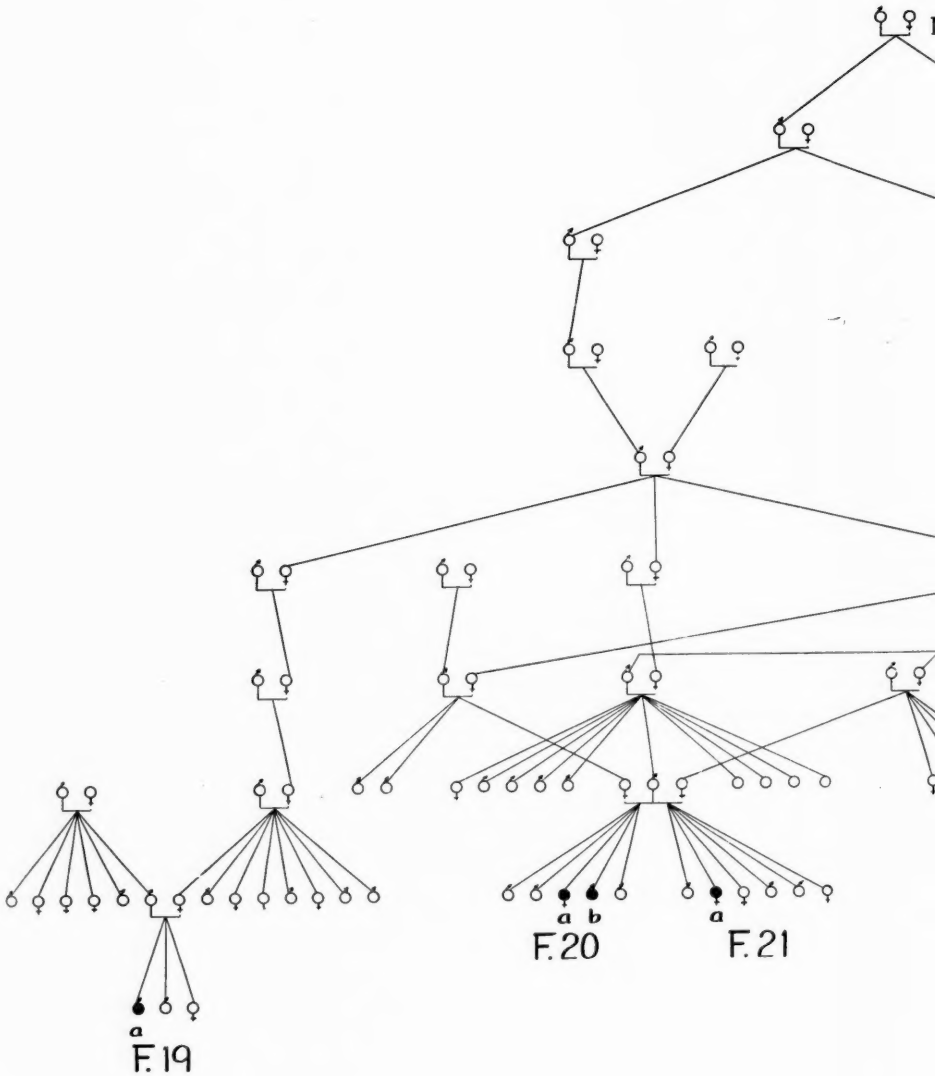

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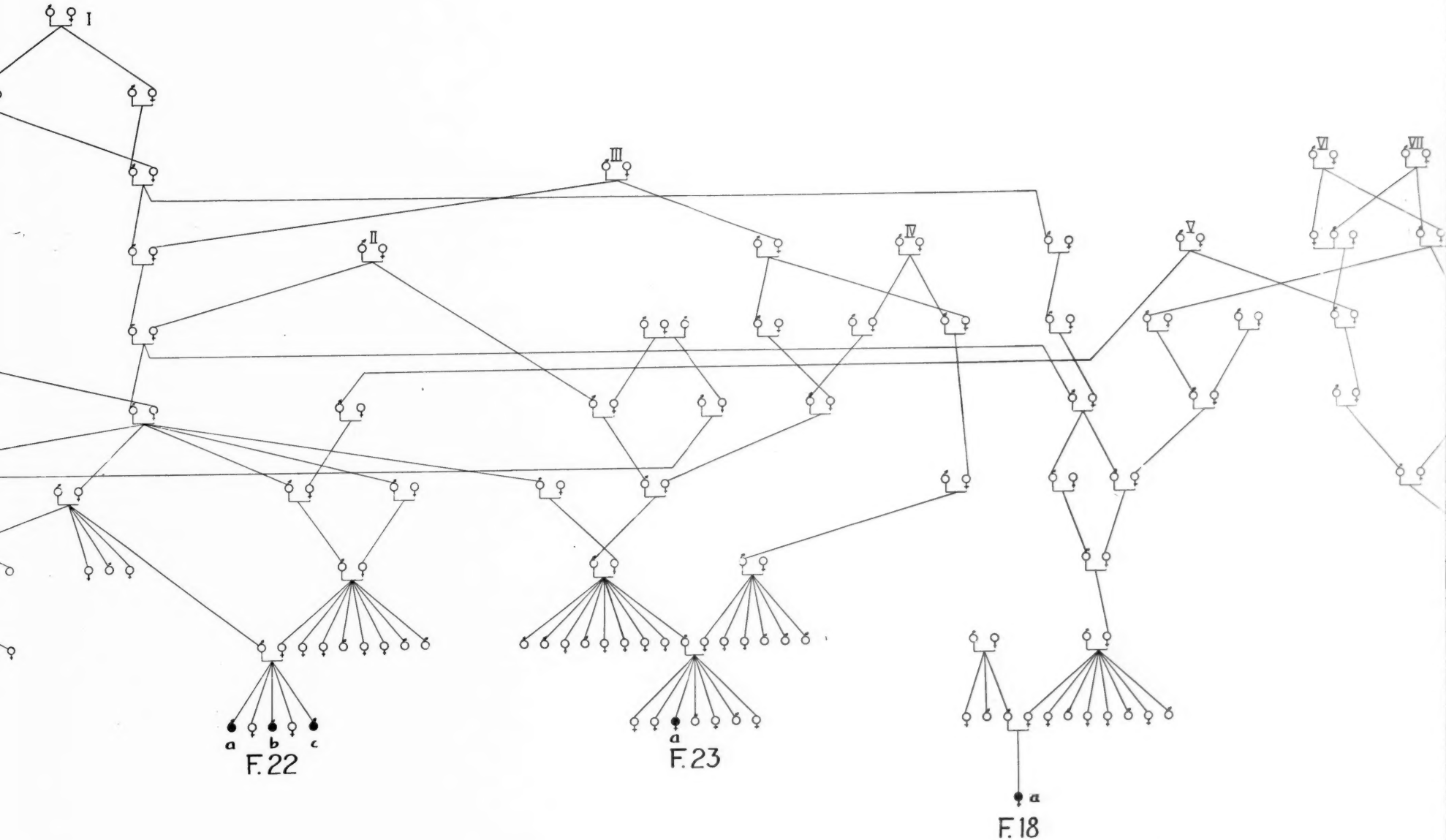

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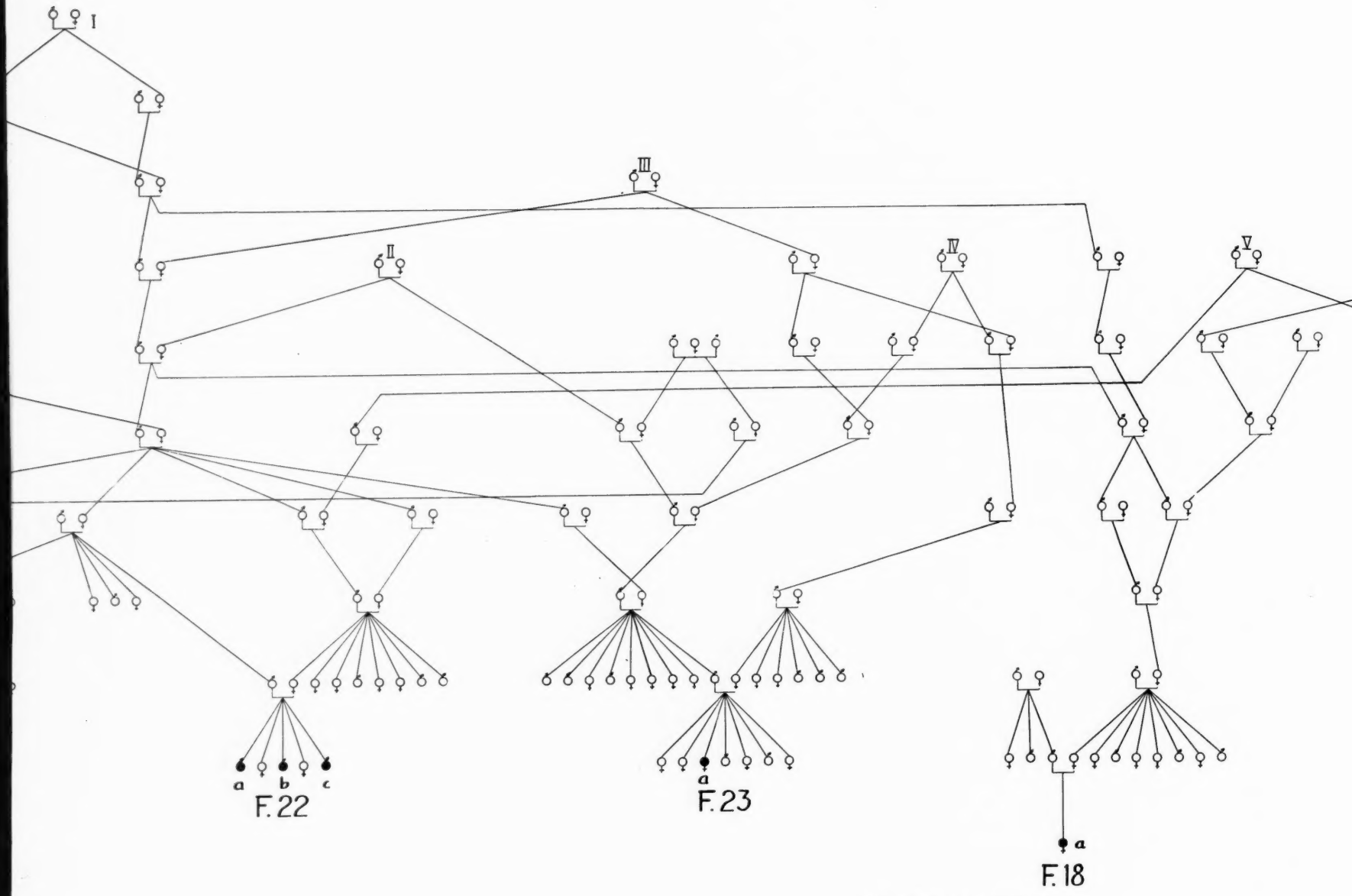

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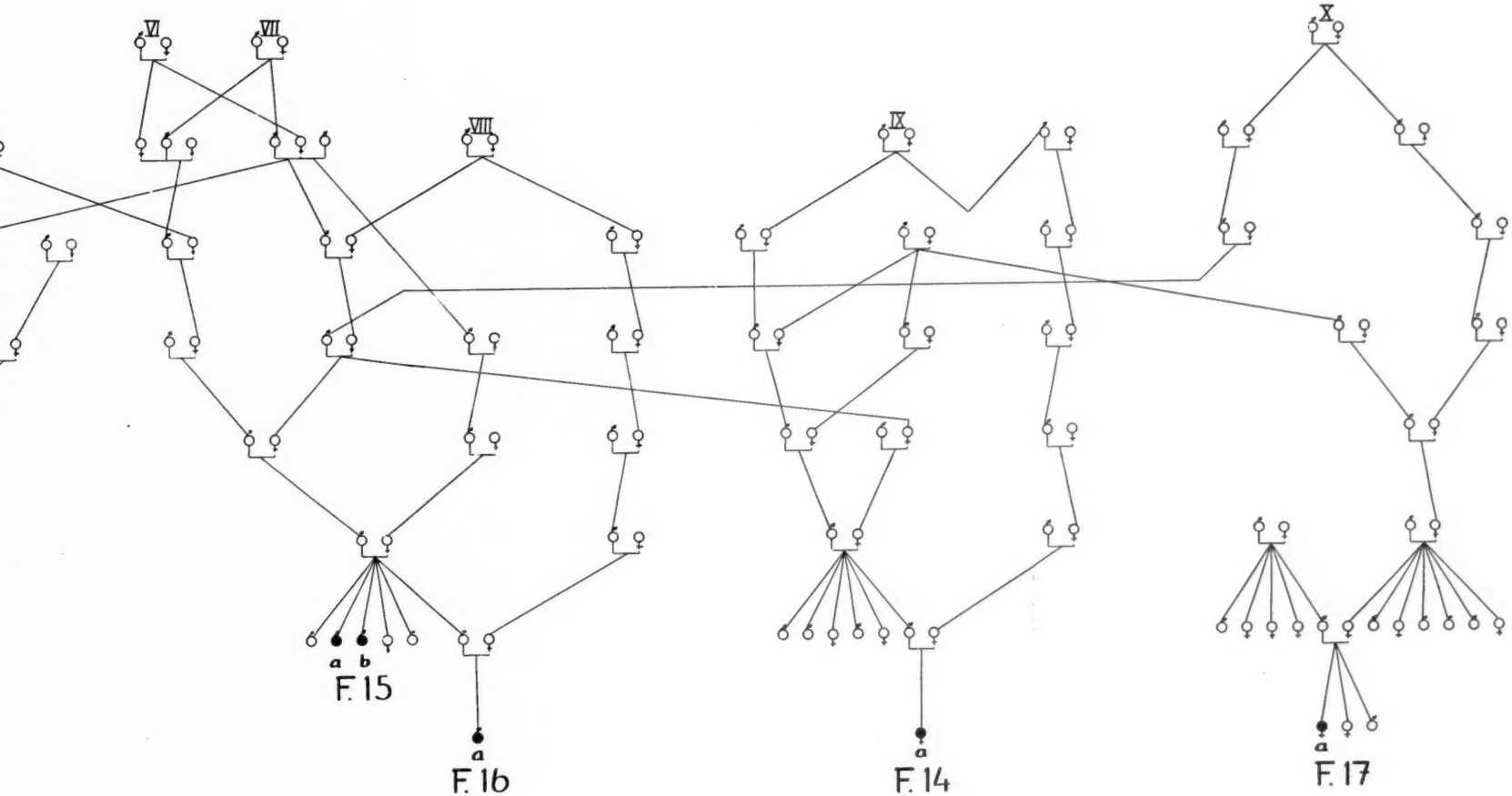

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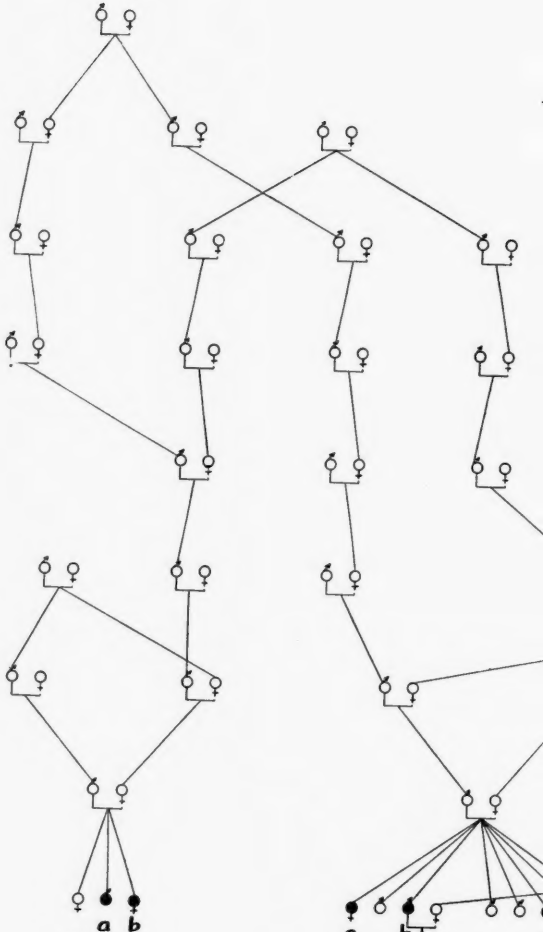
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F. 34

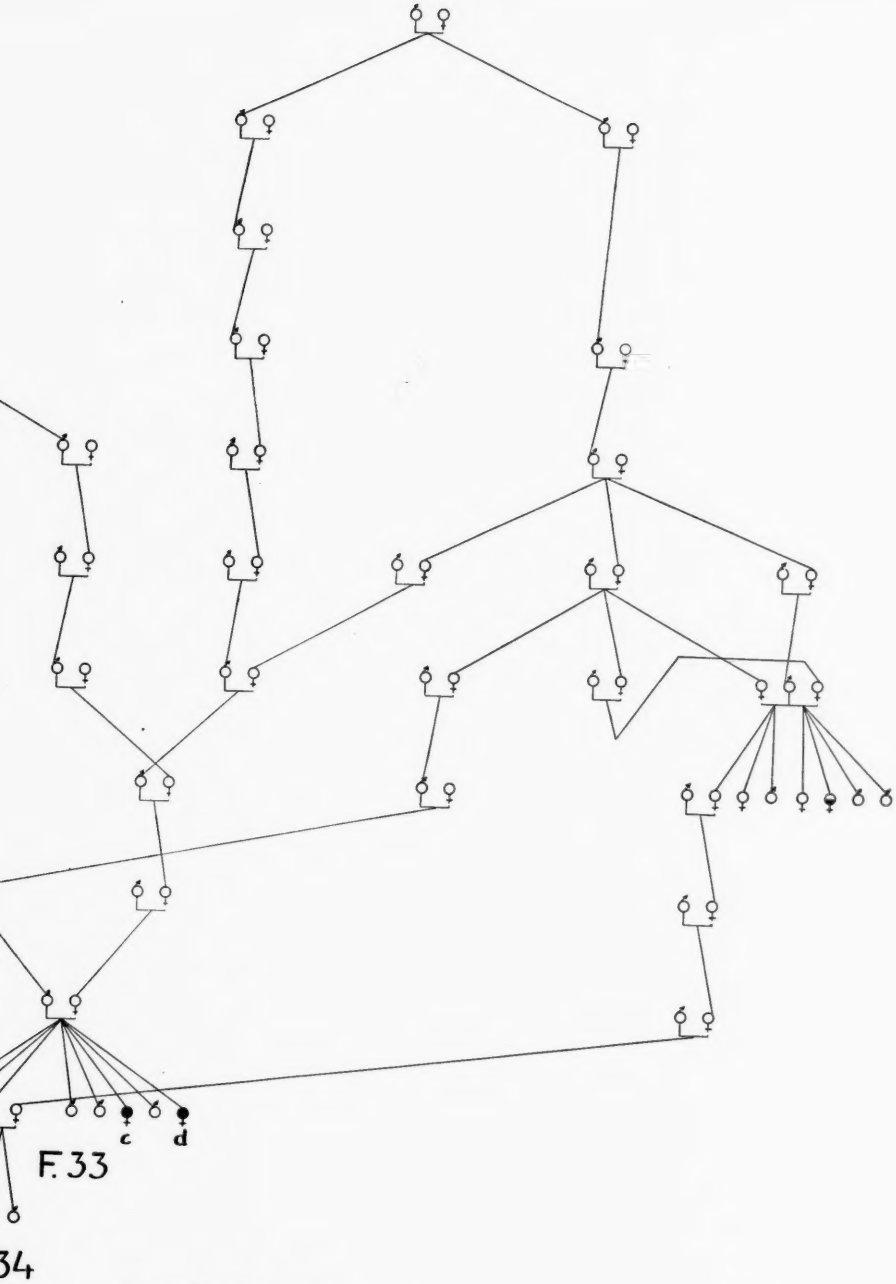

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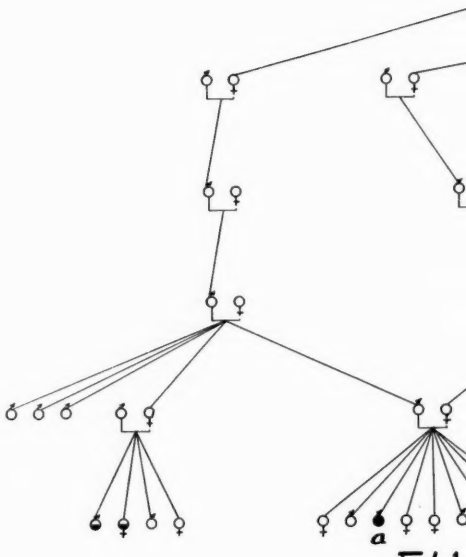
Fig. 8. The *De* complex



F. 41

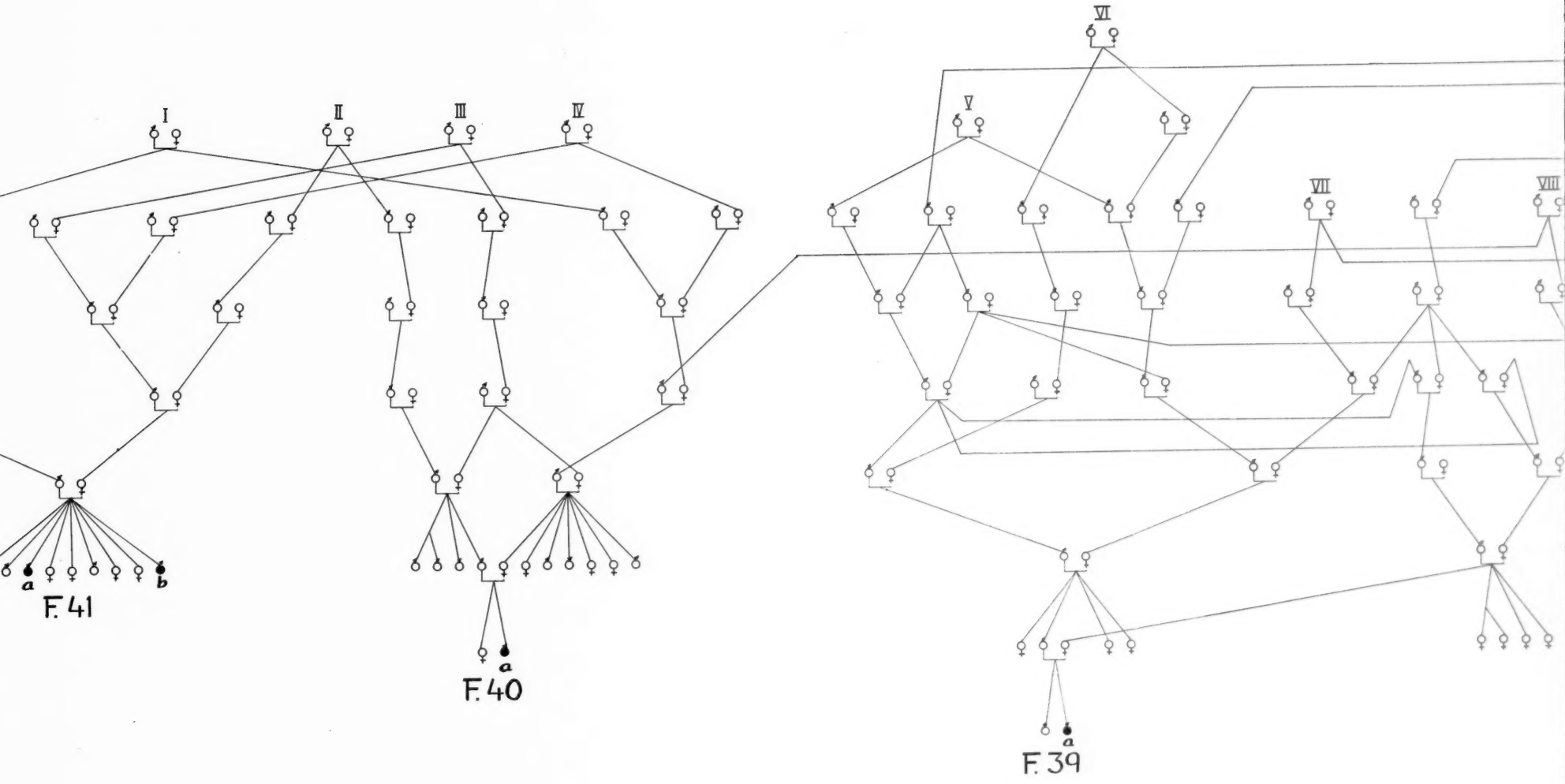


Fig. 9. The *Su* complex.

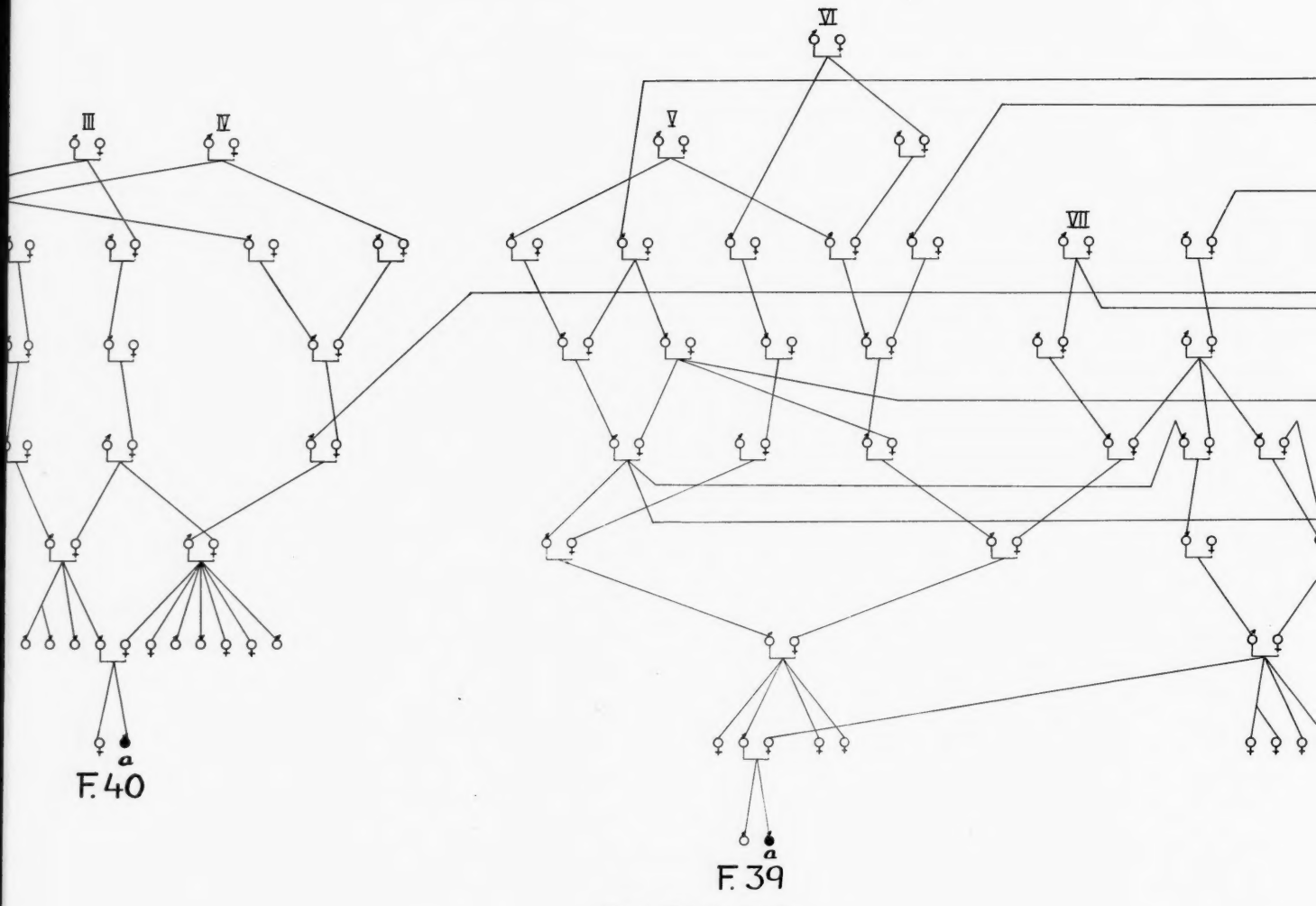
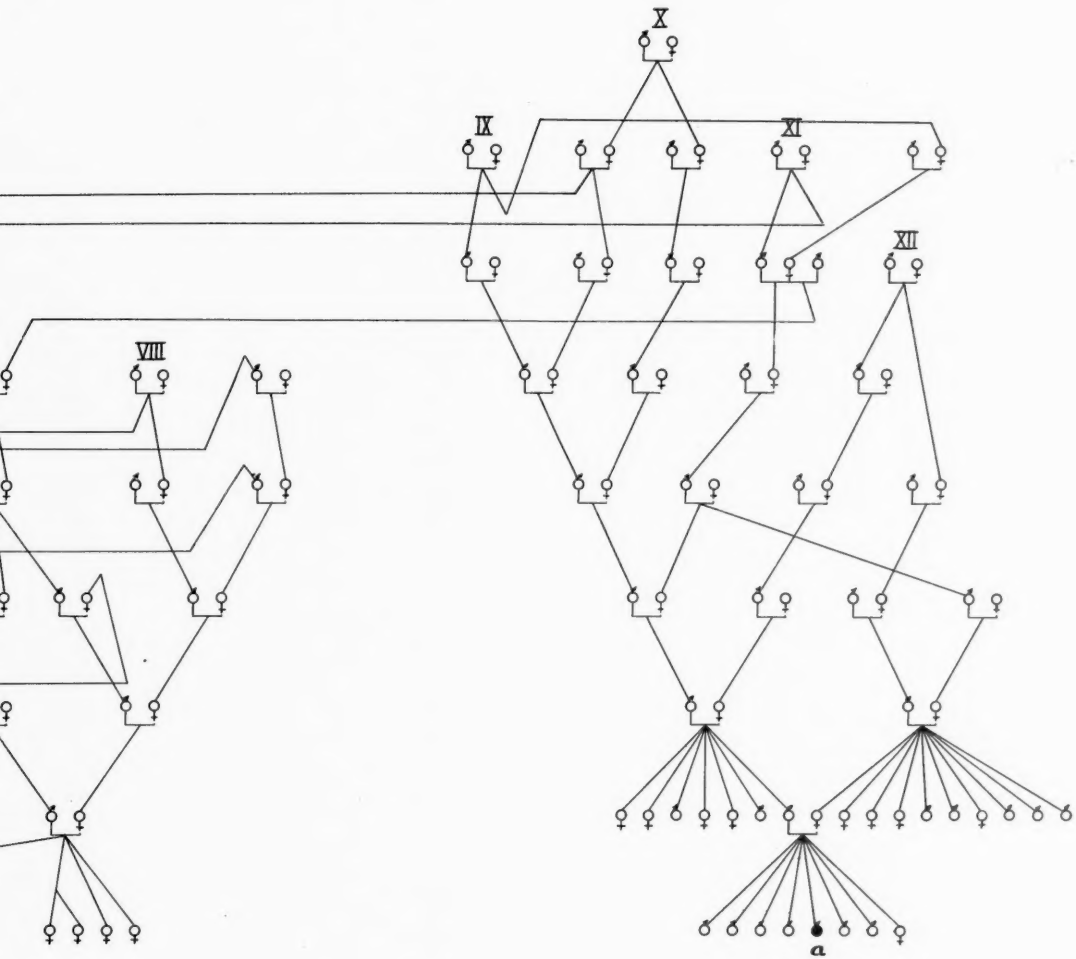


Fig. 9. The *Su* complex.



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